DISSERTATION ON

STUDY OF SERUM HIGH DENSITY LIPOPROTEIN (HDL) AS A PROGNOSTIC MARKER IN SEPSIS

Submitted in Partial Fulfillment of

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CERTIFICATE

This is to certify that the dissertation titled **"STUDY OF SERUM HIGH DENSITY LIPOPROTEIN (HDL) AS A PROGNOSTIC MARKER IN SEPSIS"** is a bonafide work done **by Dr.D.SHILPA**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfillment of the University Rules and Regulations for the award of Degree of MD General Medicine (Branch - I), Internal Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

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DECLARATION

I solemnly declare that the dissertation titled "**STUDY OF SERUM HIGH DENSITY LIPOPROTEIN (HDL) AS A PROGNOSTIC MARKER IN SEPSIS"** is done by me at Madras Medical College , Chennai – 600 003 during the period march 2016 to September 2016 under the guidance and supervision of **Prof**. **Dr. R.PENCHALAIAH M.D** submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE (BRANCH-I) .

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ABBREVIATIONS

ACCP	american college of chest physicians
AKI	acute kidney injury
APACHE	acute physiology and chronic health evaluation
ARDS	adult respiratory distress syndrome
CRP	c reactive protein
DIC	disseminated intravascular coagulation
IL	interleukin
LPS	lipo polysaccharides
MAHA	micro angiopathic hemolytic anemia
MODS	multi organ dysfunction
NF KB	nuclear factor kappa B
PAMP	pathogen associated molecular patterns
SCCM	society of critical care medicine
SIS	surgical infection society
SOFA	Seqential organ failure assessment
TLR	toll like receptors
TNF	tumor necrosis factor alpha

CONTENTS

INTRODUCTION

INTRODUCTION

Sepsis is one of the commonest cause for hospital admissions worldwide. Its a major health concern affecting millions of people around the world. In developing countries like India, infections causing more mortality and morbidity. Sepsis and related organ dysfunction reduces the quality of life of people, thereby reducing the productivity of the country.

The speed and appropriateness of therapy administered in the initial hours are likely to influence the outcome. Early recognition of sepsis before the development of organ impairment is of utmost significance. Pathophysiology of sepsis is needed for better understanding of host response to various infections and for diagnosis and treatment.

Infection causes a change in cholesterol composition. High density lipoproteins(HDL) possess several biological functions. During infections, HDL level decreases very rapidly. HDL influences humoral and innate immunity by activation of complement system and neutralisation of toxins, hence playing a critical role in sepsis. Studies have shown low levels of HDL in sepsis and its level improves with the recovery. So HDL level can help in the assessment of prognosis in patients with sepsis.

Several severity of illness scoring systems were developed and validated over years. Such scores help in stratifying the patients and help in prediction of disease outcome depending on certain clinical and laboratory parameters. These scoring systems aid in objective evaluation, improving triage, theraputic descision making, medical administration and medical auditing.

Sequential organ failure assessment (SOFA) score is one such scoring system used for sepsis related organ dysfunction severity and prognosis. Acute physiology and chronic health evaluation (APACHE) II score is widely used in critically ill patients for prognostication and mortality prediction.

In this study, HDL levels were measured in patients having sepsis . SOFA score and APACHE II score were calculated for each patient included in the study. HDL levels are correlated for patients having sepsis. Then the calculated SOFA and APACHE II scores were correlated in study sample.

AIMS AND OBJECTIVES

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Primary objective:

To study the serum level of HDL in patients with sepsis admitted in the medical wards.

Secondary objective:

1.To study the correlation of HDL levels with SOFA score.

2. To study the correlation of HDL levels with APACHE II score.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

SEPSIS

Sepsis occurs as a complication of any serious infection, which leads to various morbidity and mortality. The onset of infection causes cytokine release that produces various systemic responses like generalised vasodilatation , increased capillary permeability and leucocyte infiltration , causing generalised tissue damage. Severe sepsis can lead on to a condition termed “multi organ dysfunction syndrome (MODS)” which has a high mortality even in advanced health care units.Though there are recent advances in intensive and emergency medicine, sepsis control remains to be in great challenge.

Sepsis can present with varied manifestations and the health care providers has to be trained enough in early recognition of sepsis, its related complications and management . This is achieved by knowing the various etiologies, pathophysiology, efficent tools in diagnosis with a evidence based treatment strategies and a proper health care system at all levels.

Definition, epidemiology, pathophysiology, clinical manifestations, major complications, laboratory investigations, diagnosis and management of sepsis are disscussed in following sections. Metabolism of high density lipoprotein(HDL) , its role in sepsis, scoring systems like sequential(sepsis-related) organ failure assessment(SOFA) score and acute physiology and chronic health evaluation II(APACHE II) score and their importance are to be disscussed in the following sections.

HISTORY OF SEPSIS

Hippocrates (ca.460- 370 BC) was the first person to use the term “Sepsis” which was derived from the Greek word “sipsi” that means “ make rotten ” . During 1000 BC , Ibn Sina found that fever and “ putrefaction of blood ” were interrelated to each other.

In seventeenth century Hermann Boerhave derived that sepsis was caused by the toxic substances present in the air. In the early nineteenth century Justus Von Liebig explained the reason that sepsis is due to the contact between oxygen and wounds. In the 18^{th} century, Semmelweis discovered the co-relation between contaminated hands and puerperal infections. He showed that a simple procedure like hand washing by

using chlorinated lime solution before a gynaecological examination will decrease the incidence of puerperal sepsis.

Louis Pasteur discovered microbes and also said that these microbes could cause disease. He also explained that these microbes in fluids can be destroyed by heating and thus the concept of sterilisation was born. Joseph Lister did landmark studies in the field of anti septic management with carbolic acid (known as the antiseptic method). The German physicians Lennhartz and Schottmuller proposed that sepsis is spreading into the blood stream from the primary source of infection through the bacterial toxins rather than the bacteria per se.

In the pre antibiotic era, death rate was high in sepsis. Those patients were observed to have a low blood pressure, which was termed as septic shock. After the second world war, antibiotics were introduced, since then sepsis mortality was reduced.

In the late nineteen sixties , Asbough noted that severe sepsis could result in intense inflammatory response , particularly in the respiratory system causing diffuse alveolar infiltrates, known as Adult Respiratory Distress Syndrome (ARDS). Similar studies showed that sepsis occurs

secondary to a dysregulated immune response and not merely by the direct toxic effects of the microbes.

With the advent of various micro organisms and introduction of novel antibiotics, sepsis management flourished to greater extent. In the year 1991, an international consensus conference was organised by the american college of chest physicians (ACCP) and the society of critical care medicine (SCCM), where the spectrum of sepsis and allied conditions were defined[1].

The revision of this was done in 2001. The surviving sepsis campaign were published in 2004 and revised in 2008. In the year 2012, these guidelines were updated[2]. In 2016, the third international consensus definitions for sepsis and septic shock(sepsis-3) was released[3].

DEFINITIONS

Based on the consensus among international experts specific definitions of sepsis and its related conditions have been defined.

SIRS or systemic inflammatory response syndrome[4] may be defined as the presence of two or more of the following variables

1) Temp < 36 or >38.3 degree Celsius
2) Heart rate > 90
3) Respiratory rate > 20
4) WBC count > 12, 000 or < 4,000 or band forms more than 10 %

The term *infection* refers to the presence of micro organisms in an otherwise normally sterile body cavity or fluid (eg Urinary Tract) or the presence of an inflammatory response to microbes in body cavity or fluid that normally harbour micro organisms (eg GIT).

Sepsis may be defined as the presence of two or more criteria of SIRS in the context of a documented or clinically suspected infection .

But the diagnostic criteria of sepsis was further modified in 2001 - international conference convened by the Society Of Critical Care Medicine (SCCM) , European Society of Intensive Care Medicine (ESICM) , American College Of Physicians (ACCP) , American Thoracic Society (ATS) and Surgical Infection Society (SIS)[5]. It includes the following parameters , as shown in the following table

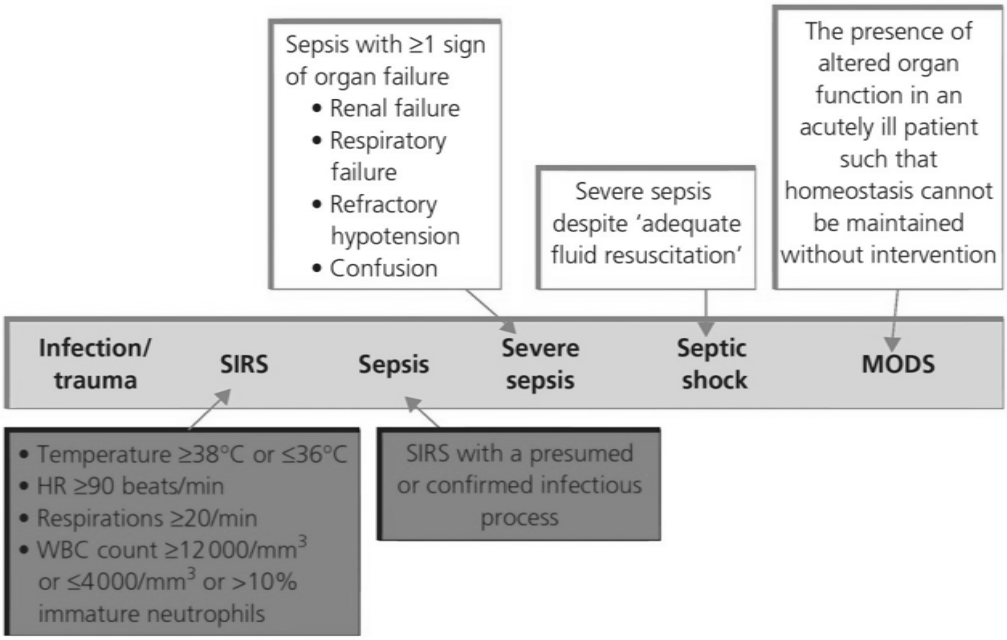
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90/min or >2 SD above the normal value for age
Tachypnoea: >20/min
Altered mental status
Significant oedema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycaemia (plasma glucose >120 mg/dl or 6.7 mmol/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12 000/μl)
Leukopenia (white blood cell count <4000/μl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above normal value
Plasma calcitonin >2 SD above the normal value
Haemodynamic parameters
Arterial hypotension (SBP <90 mmHg, MAP <65 mmHg, or a decrease in SBP >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation <65%
Central venous oxygen saturation <70%
Cardiac index >3.5 l/min
Organ dysfunction parameters
Arterial hypoxaemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5 ml/kg/h for ≥2 h)
Creatinine >176.8 mmol/l
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100 000/μl)
Hyperbilirubinemia (plasma total bilirubin >34.2 mmol/l)
Tissue perfusion parameters
Hyperlactataemia (>2 mmol/l)
Decreased capillary refill or mottling

Septic shock is defined as the presence of persistent hypotension despite adequate fluid resuscitation[6].

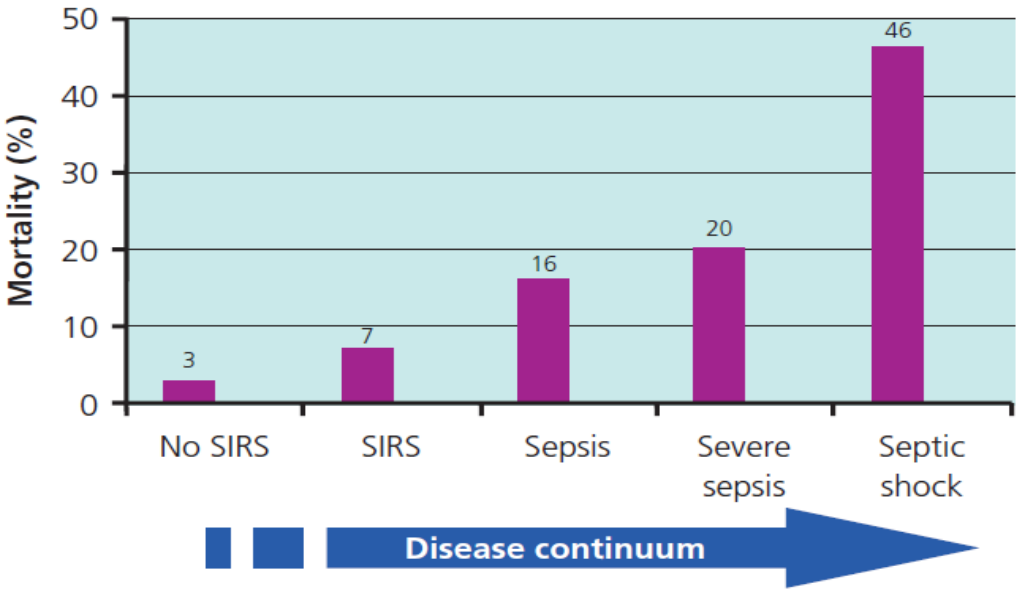
MODS or Multi Organ Dysfunction Syndrome[7] may be defined as the clinical syndrome which is associated with progressive and potentially reversible dysfunction of two or more organ systems.

Thus the above told terms belong to the continuous spectrum of sepsis.

THE SPECTRUM OF SEPSIS AND ASSOCIATED MORTALITY



SEPSIS – A DISEASE CONTINUUM



According to the Third International consensus Definitions for Sepsis and Septic Shock (Sepsis – 3)[8], released in 2016 recommends new terms and definitions as given in the box below. The concept of SIRS was universaly declared by the task force to be unhelpful.This consensus recommends SOFA score for defining sepsis. SOFA score is calculated as shown in the table below.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

*At least 2 of the above should present for rapid identification of suspected sepsis patients.

New Terms and Definitions

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.

The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.

A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Nonspecific SIRS criteria such as pyrexia or neutrophilia will continue to aid in the general diagnosis of infection. These findings complement features of specific infections

Terminology and *International Classification of Diseases* Coding

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

Abbreviations: *ICD*, *International Classification of Diseases*; MAP, mean arterial

EPIDEMIOLOGY

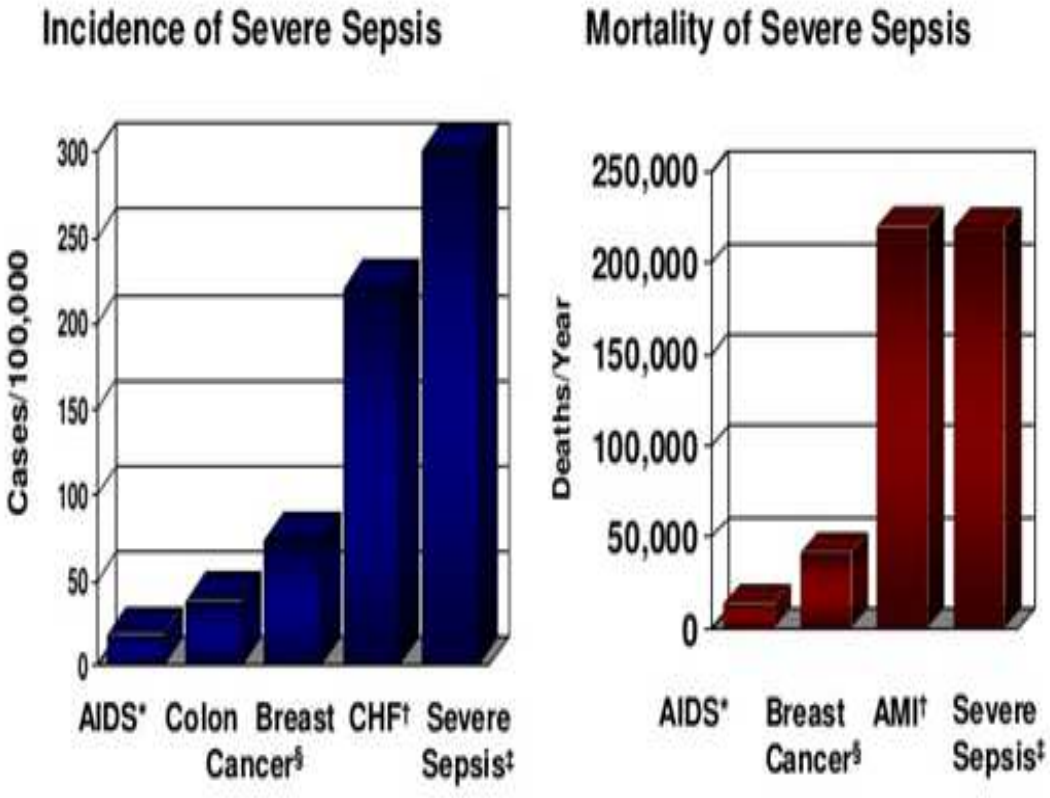
According to the world sepsis declaration 2016, sepsis is the most common and less noticed illness in the world. Around the world, 20 to 30 million people are found to be affected by sepsis related illness every year. Among these 6 million cases are of neonatal and childhood sepsis and around 100,000 cases due to maternal sepsis. Globally one person dies due to sepsis every few seconds.

To address the global burden of sepsis, the need for prevention and effective management of sepsis, the Global Sepsis Alliance and the World Sepsis Day movement joined with national and international bodies and other allied groups are working together .The first World Sepsis Congress was organised as an online congress on september, 2016. World sepsis day is conducted every year on september 16. The mortality rate of severe sepsis is nearly 50%. The incidence of sepsis and its related complications are increasing because of the following:

1. Aging population
2. Multiple comorbid conditions
3. increased immunosuppressive states
4. Expanding spectrum of micro organisms

In developed countries sepsis is increasing by an annual rate of 8 to 13% during the last decade, because of increasing age, more use of high risk interventions in all age group, with the development of drug resistant and virulent organisms[9].In developing countries, malnutrition, poverty, lack of accsess to vaccines and timely treatment favours death. Sepsis , as a cause of mortality ranks much higher than the other major killer diseases as illustrated by the following picture[10].

INCIDENCE OF SEPSIS COMPARED WITH INCIDENCE OF OTHER MAJOR DISEASES



Angus DC et al Critical care medicine 2010

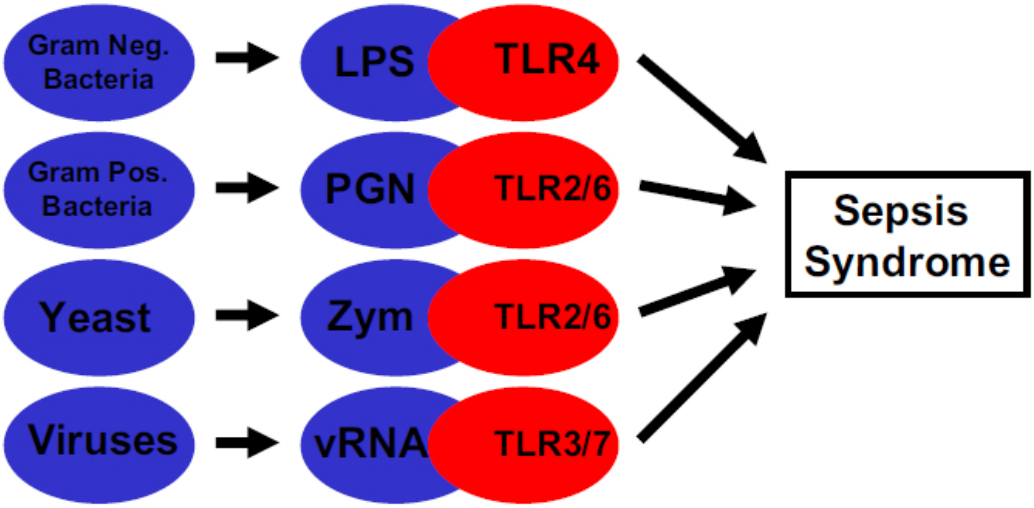
CHF - Congestive heart failure , AMI - Acute Myocardial Infarction

PATHOPHYSIOLOGY OF SEPSIS

Sepsis is due to the complex interplay between the infective pathogen and the host immune system. The innate immune system which acts as the first tier of defence against the invading organism, is primarily responsible for the sequence of inflammatory responses that falls under sepsis. The innate immune system consists of monocytes, macrophages, natural killer cells , endothelial cells and the dendritic cells. When the pathogenic organism enters the body , it activates this non specific innate immune response through the *Toll like receptors* (TLR). These receptors are so named because they resemble the *toll receptors* found in Drosophila.

The TLRs bind to proteins known as Pathogen Associated Molecular Patterns (PAMP). They are highly conserved sequences found in various micro organisms. The PAMPs are generally composed of lipo-polysaccharides or LPS (in Gram negative organisms) and petidoglycans (in Gram positive organsisms). The TLR sends intra cellular signals for the activation of transcription factors like the nuclear factor kappa b (NF KB). Then there is a production of inflammatory molecules like the interleukins (IL-1 , 6 , 8) , tumor necrosis factor alpha , cyclo oxygenases and prosta glandins. This is followed by the

secondary adaptive immune response mediated by the T lymphocytes and B lymphocytes. The binding between the TLR and the PAMPs are shown in the following picture

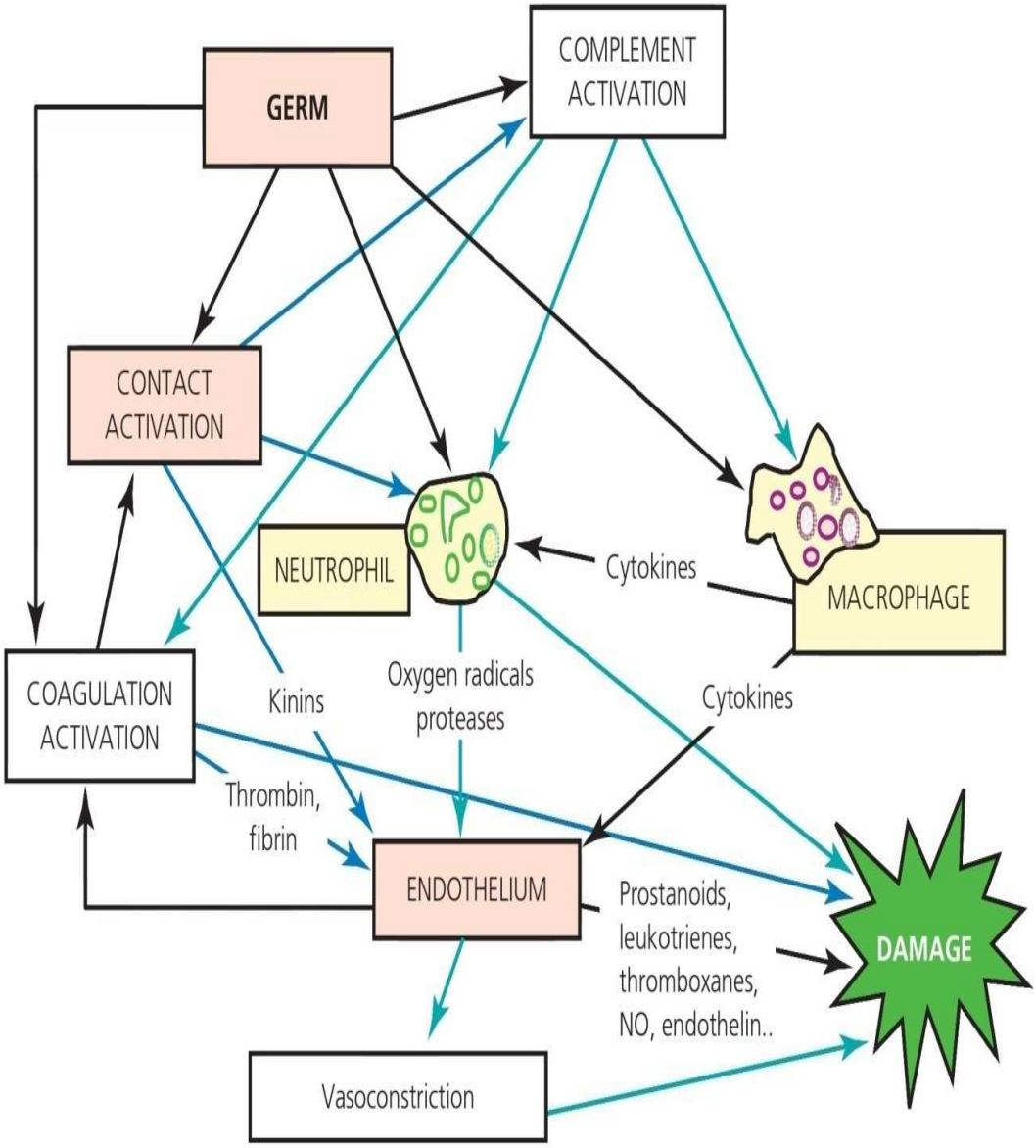


There are more than 10 TLRs each having an affinity for different antigen. Among them the most important is the TLR 4 which binds to the lipopolysaccharide component of Gram negative organisms and thus playing an important role in pathogenesis due to Gram negative septicemia. It is also important to note that even endogenous substances like heparin sulphate , hyaluronate , fibronectin , heat shock proteins , fibrinogen and certain polymeric sugars may also stimulate the TLR pathway. This is the reason for development of a systemic inflammatory response in the absence of an infection ,in situations like pancreatitis. Few of the common TLRs and their specific ligands are depicted in the subsequent figure.

TLR	Ligands
TLR1 (heterodimer with TLR2)	Triacylated lipopeptides, lipomannans from *Mycobacterium tuberculosis*
TLR2 (often dimer with TLR2 or 6)	Lipoproteins, peptidoglycans, lipoteichoic acids, yeast zymosan
TLR3	Double-stranded RNA
TLR4 (homodimer plus CD14 and MD2)	LPS, heat shock proteins, pneumolysin, respiratory syncytial virus coat proteins, heparan sulphate fragments, fibrinogen peptides
TLR5	Flagellin
TLR6 (heterodimer with TLR2)	Diacylated lipopeptides
TLR7	Responds to synthetic nucleosides and imidazoquinoline antivirals; native ligand is thought to be single-stranded RNA in endosomes
TLR8	Same as for TLR7
TLR9	Bacterial DNA—unmethylated CpG motifs
TLR10	Ligand unknown but TLR10 expressed in lung and B lymphocytes
TLR11	Uropathogenic bacteria in mice; absent in humans

The invading pathogen interacts with innate immunity, adaptive immunity, the vascular endothelium and the coagulation pathways to produce the septic response.

PATHOGENESIS OF SEPSIS

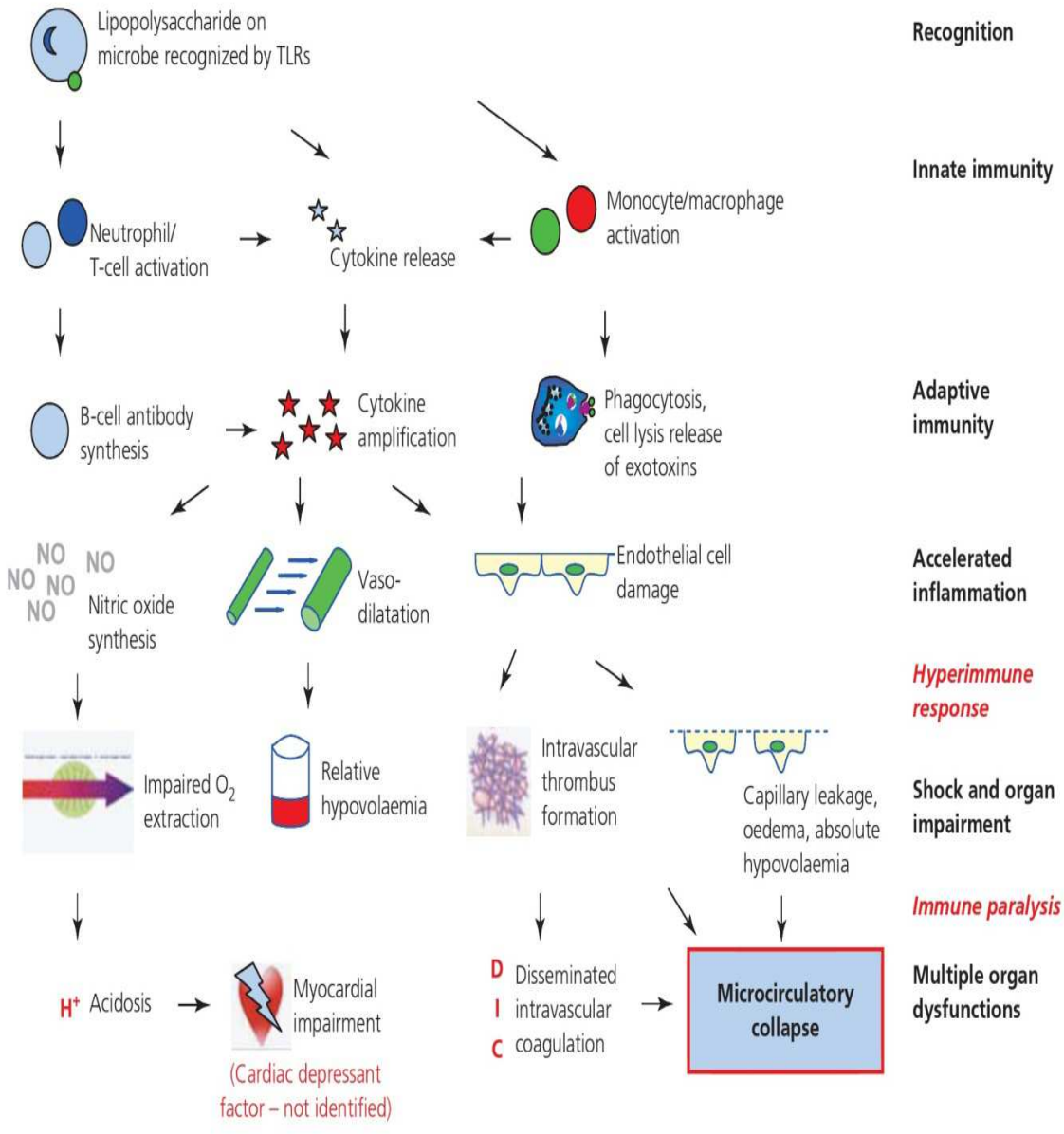


ROLE OF VASCULAR ENDOTHELIUM

The vascular endothelium plays a vital role in the pathogenesis of sepsis. The endothelial cells are stimulated either directly by the bacteria or by the bacterial products. The response of the endothelium is dependent on the age of the patient , gender , co-morbid conditions , host genetic factors and on the characteristics of the invading microbes. Disruption of the endothelial function results in structural and functional alterations which leads to the following effects like

- Uncontrolled release of vaso active substances like nitric oxide and prostacyclins
- Hyper reactivity of the vascular smooth muscles in response to vaso constrictors
- Adhesion and Migration of leucocytes
- Platelet activation and aggregation
- Imbalance between pro coagulants and anti coagulants
- Increased pro apoptotic substances
- Loss of barrier function

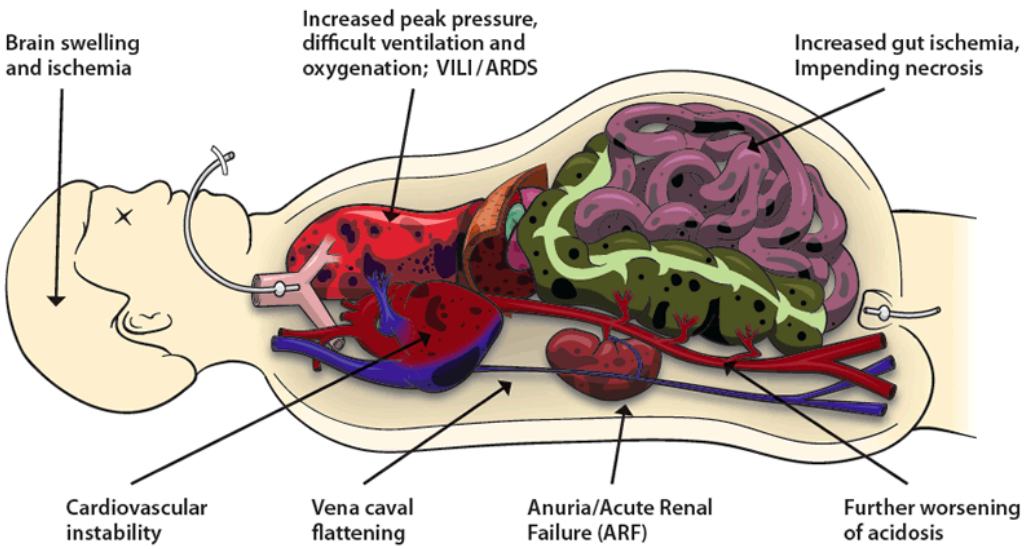
Hence the septic response is secondary to a complex interaction between the components of the pathogen (eg – Lipo polysaccharides , peptide glycans) and the host factors (innate & adaptive immunity , endothelial dysfunction) as illustrated in the image below



ORGAN DYSFUNCTION IN SEVERE SEPSIS

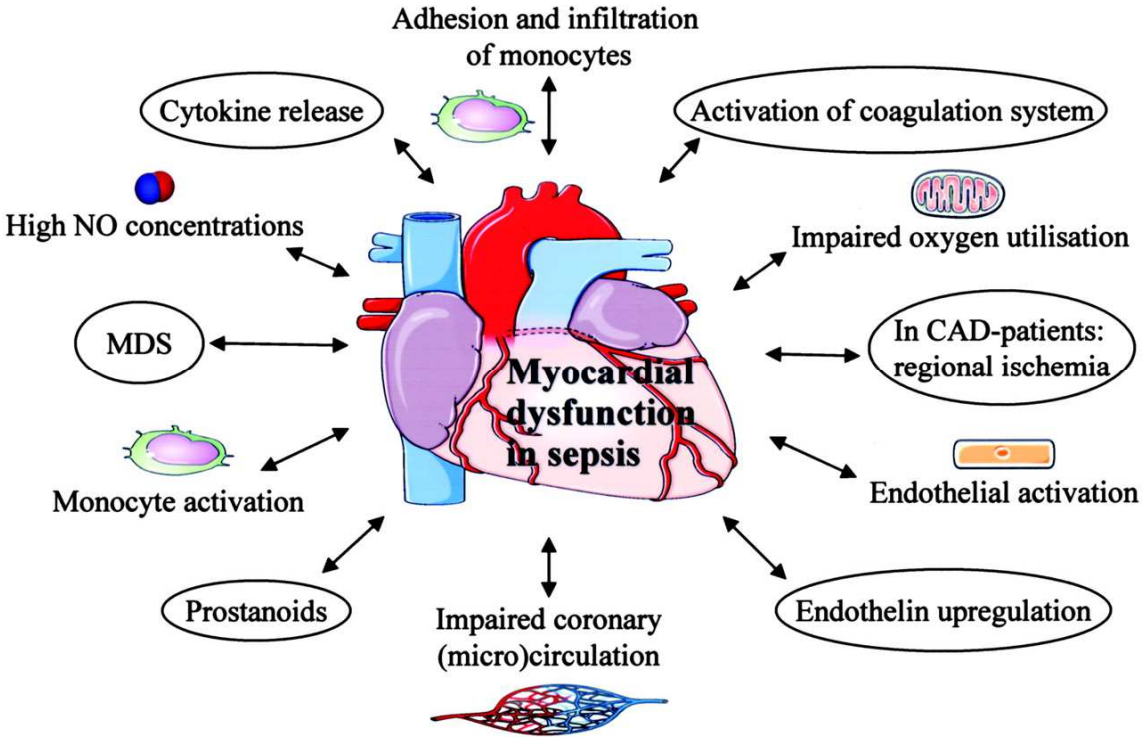
Sepsis results in a detrimental effect to major organs in the body like the central nervous system , cardio vascular system , coagulation pathways , gastro intestinal system , renal system , respiratory system and the immune system. Dysfunction of two or more organ systems is known as Multi Organ Dysfunction Syndrome (MODS). The onset of MODS is associated with a very high mortality if associated with immune suppression , resistant organisms, advanced age and comorbid conditions.

SEPSIS -- MULTI ORGAN FAILURE



CARDIO VASCULAR SYSTEM

During 1951, Waisbren et al was the first person to describe the myocardial dysfunction seen in sepsis. The reduced systemic resistance found in sepsis initially masks the reduced myocardial contractility. As the disease progresses there will be frank manifestation of the reduced stroke volume and ejection fraction. Cardiovascular dysfunction in sepsis has significant role in increase of mortality rates. Global vaso dilatation, increased capillary permeability and myocardial depression leads to a state of tissue hypo perfusion which is indicated by the elevated lactate levels.



RENAL SYSTEM

Renal failure is seen in nearly 20 % cases with severe sepsis. Sepsis is remained to be the commonest cause for Acute Kidney Injury (AKI) in the intensive care units. The conventional methods used in the detection of AKI namely urinary casts and fractional excretion of sodium are not adequate to make an early diagnosis of sepsis related AKI. Because of this newer bio markers like Neutrophil Gelatinase Associated Lipocalin (NGAL), cystatin C, urinary interleukin 18 and Kidney injury molecule (KIM 1) are now used in detectig AKI. Some of these bio markers may even differentiate between septic AKI and non septic AKI.

Sepsis causes AKI through several pathways like direct inflammatory injury, ischemia reperfusion injury, dysregulated coagulation, endothelial cell dysfunction and accelerated apoptosis. The elevated levels of pro inflammatory substances in sepsis such as TNF alpha , interleukins and iterferons exert a direct toxic effect on the glomerular cells and the renal tubular epithelium. The higher levels of nitric oxide leads to generalised vaso dilatation with secondary hypotension and activation of the renin – angiotensin axis which causes intra renal vasoconstriction and thus the fall in glomerular filtration rate. Hypotension , intra vascular hypovolemia , renal vaso constriction and the cytokine storm lead on to acute tubular necrosis. Hence there is a

multi directional injury to the renal parenchyma which needs an immediate renal replacement therapy.

Some of the treatment aspects in sepsis related AKI are given below :

- Volume repletion and ionotropic support to maintain a mean arterial pressure of atleast 65 mm Hg and a central venous pressure of 8-12 mm Hg
- The vasopressors like nor epinephrine and vasopressin that are found effective in septic shock. They should be started as early as possible in septic shock
- Optimal blood glucose control using regular insulin
- Fenoldopam , a dopamine agonist has shown improvement in renal blood flow and can be tried
- Activated protein C will decrease the thrombin load and hence modulate the endothelial dysfunction. But the trials were proved to be ineffective
- N acetyl cysteine and Atrial Natriuretic Peptide have been found to have useful in septic AKI
- Newer therapeutic intrventions like the use of TLR inhibition , suppression of the inducible nitric oxide synthase pathways , caspase inhibitors , lysophosphatidic acid and use of mesenchymal stem cells

- Early initiation of extra corporeal purification of blood which is having an extra advantage of removal of excess cytokines
- Hemofiltration , hemadsorption and renal assist devices have been tried

CENTRAL NERVOUS SYSTEM

Many patients of severe sepsis develop a septic encephalopathy having manifestations like delirium, confusional states and coma.

The development of septic encephalopathy is contributed by the following

a) disruption of the blood brain barrier

b) intra cranial hemorrhage (due to DIC)

c) micro infarcts

d) hypoxic encephalopathy

e) cytokine excess and

f) development of metastatic abcesses

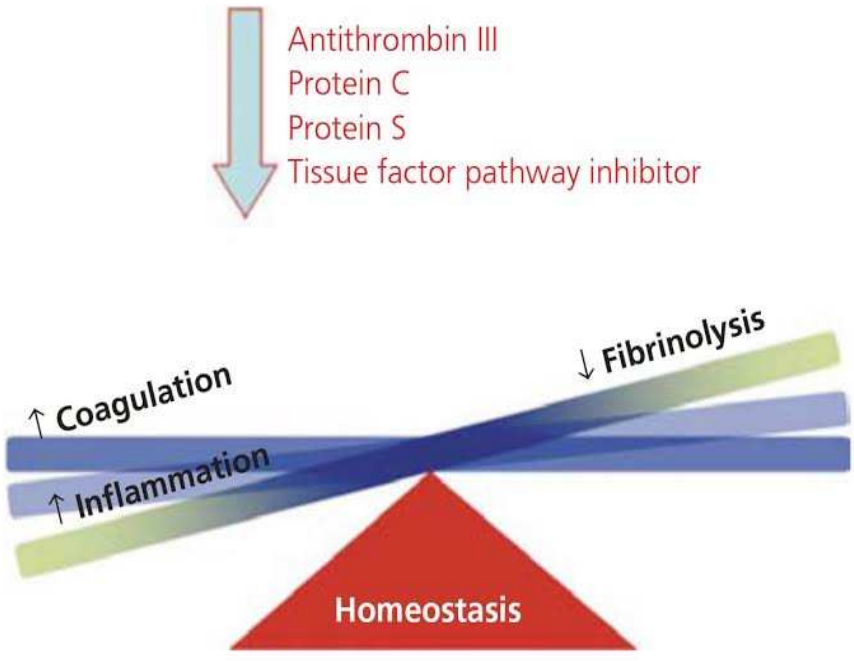
Septic encephalopathy can results in residual neurological sequelae. They have more potential to develop critical illness polyneuropathy. This is because of the sensori motor axonal degeneration which is characterised by hypotonic limbs and diminished reflexes. Depression and anxiety neuroses are more common in these people due to the psychological impact of prolonged ICU stay.

GASTRO INTESTINAL SYSTEM

Severe sepsis causes decrease in blood pressure which may lead to reduced perfusion pressure in the splanchnic circulation which induces liver dysfunction. Bacterial translocation occurs from the gut and endotoxemia. Generally such translocated bacteria and their products will be destroyed by the reticulo endothelial system of the liver. Because of hepatic ischemia in sepsis these toxins enter the systemic circulation directly and exert its inflammatory effects.

COAGULATION PATHWAYS

An imbalance between the pro thrombotic and anti thrombotic factors occur , as shown in the following picture



Coagulation pathways are affected in gram negative sepsis in which endothelial dysfunction leading to disseminated intravascular coagulation (DIC). It is a consumption coagulopathy with the presence of thrombotic and hemorrhagic problems. This will lead to complications of micro angiopathic hemolytic anemia (MAHA) , acute renal failure and intra cranial hemorrhages and infarcts.

IMMUNE DYSFUNCTION

Sepsis is so severe enough to dysregulate the immunological pathways through the cytokine release thereby resulting in a state of relative immuno suppression.

CUTANEOUS MANIFESTATIONS

Sepsis, will either directly or by means of disseminated intra vascular coagulation leads to skin lesions like petechiae , purpurae , vesicles , blisters , necrosis and gangrene. The disruption of dermal blood vessels by the micro thrombi will affect dermis. The cutaneous necrotic hemorrhagic lesion known as purpura fulminans is notoriously common in septicemia due to Neisseria meningitidis and streptococcus pneumoniae.

Musher said that “there are mainly three patterns of involvement of the skin in Gram negative sepsis”.

1) Cellulitis and thrombophlebitis

2) Ecthyma gangrenosum in cases of impaired inflammatory response due to neutropenia

3) Symmetrical peripheral gangrene associated with disseminated intra vascular coagulation.

Palpable petechiae and purpurae are due to leukocytoclastic vasculitis, which are associated with organisms like Neisseria, pneumococci and staphylococcus aureus. “A diffuse erythematous picture” called *erythroderma* seen in toxic shock syndrome caused by staphylococcus aureus or streptococcus pyogenes. After two weeks desquamation of the skin may occur .

RESPIRATORY SYSTEM

In many cases of sepsis, initial presentation may be hyperventilation with respiratory alkalosis. In which alveolar and interstitial fluid accumulation assoociated with the recruitment of the inflammatory cells and cytokines. This results in the disruption of the alveolar membrane. Indeed there is a proliferation of the Type II pneumocytes which replaces the Type I cells with concomitant surfactant decrease. Rapid increase of alveolar exudates, fluid accumulation in the interstitium and the fibrotic changes ultimately leading to most dreaded

complication the so called “Acute Respiratory Distress Syndrome (ARDS)” .

The following are the salient feautres of ARDS -

I. Onset of a lung injury within one week of the known clinical insult

II. Chest X ray showing Bilateral opacities

III. Fluid overload related to cardiac problems to be ruled out

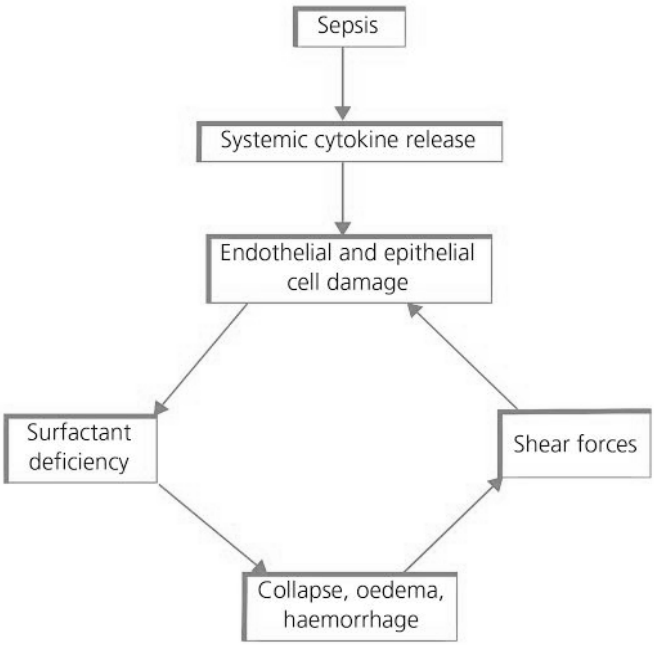
IV. Presence of hypoxemia

The term “*acute lung injury*” has been replaced by the newer Berlin definitions by varying grades of ARDS. The grading system is based on the pAO2 / FiO2 ratios.

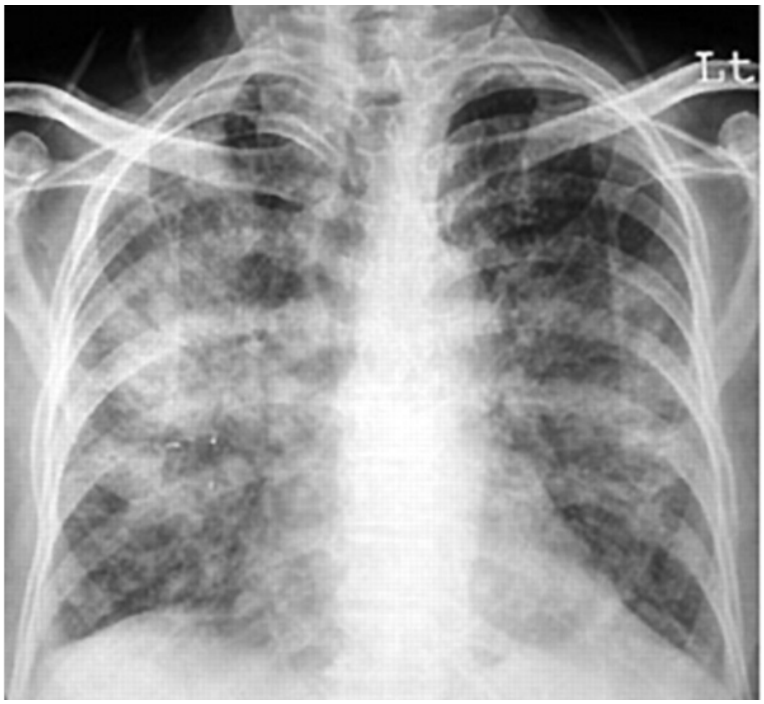
Thus ARDS is classified as

1. Mild ARDS - pAO2 / FiO2 : 200 to 300
2. Moderate ARDS - pAO2 / FiO2 : 100 to 200
3. Severe ARDS - pAO2 / FiO2 : < 100

SEPSIS – ARDS PATHWAY



CHEST X RAY – ARDS



INVESTIGATIONS TO BE DONE IN SEPSIS

The investigations are done to assess the following factors

1. Source of infection
2. Severity of infection (especially the organ dysfunction)
3. Causative micro organisms
4. Prognostication

First, the basic investigations are done. The complete blood count may show leucocytosis or cytopenias. The serial monitoring of cell counts gives an idea about the response to treatment. Septic conditions have neutrophilic leucocytosis, typically. However certain infections like typhoid , brucellosis , Rocky mountain spotted fever , ehrlichiosis etc may have peripheral blood leukopenia.

The liver function tests, renal function tests , coagulation profile and arterial blood gas analysis are done to assess the presence and extent of organ dysfunctions. Most Often, unexplained hyperbilirubinemia, hyper lactatemia, metabolic acidosis, respiratory alkalosis or a thrombocytopenia are the earliest markers of septic process. Radiological investigations (chest X ray, X ray- paranasal sinuses, ultrasound of abdomen , CT and MRI imaging of relevant areas , echocardiography) are very useful in localising the source of infection. If the facilities are available cytokine and bio marker assay may be done.

Blood cultures and cultures of relevant tissue or fluids (including pus, sputum, CSF, urine, stool, bone marrow, skin lesions) are to be taken before starting the antibiotics. The blood cultures are taken from two or three different venipuncture sites. The volume should be atleast 23 – 30 ml for blood culture. Microscopic examination and Gram staining / AFB staining of the infected fluids or tissue samples may also be done. Molecular assays such as polymerase chain reaction will be more specific.

Acute phase reactants like C Reactive Protein (CRP) , procalcitonin[11],[12] and the erythrocyte sedimentation rate (ESR) are helpful in assessing the severity of sepsis and its response. Critical illness associated adrenal insufficiency can be diagnosed with the help of baseline serum cortisol and ACTH levels.

Better descision making by the physician is by the assessment of the prognosis in severe sepsis . Serum lactate levels and serum pro calcitonin are particularly useful for prognostication. Prognostic scores have been formulated based on some of the common blood investigations and clinical variables to guide the treating intensivist.

DIFFERENTIAL DIAGNOSIS OF SEPSIS

Several conditions can produce a state of hypotension , raised body temperature and features of multi organ dysfunction and hence mimic sepsis. Some of them are listed below :-

1. Trauma
2. Burns
3. Adrenal insufficiency
4. Pancreatitis
5. Drug overdose or drug reaction
6. Ruptured or dissecting aneurysm of aorta
7. Thyroid storm
8. Pulmonary embolism
9. Occult internal bleed
10. Cardiac tamponade
11. Serotonin syndrome
12. Heat stroke
13. Anaphylaxis
14. Post cardio pulmonary bypass
15. Malignant hyperthermia

MANAGEMENT OF SEPSIS

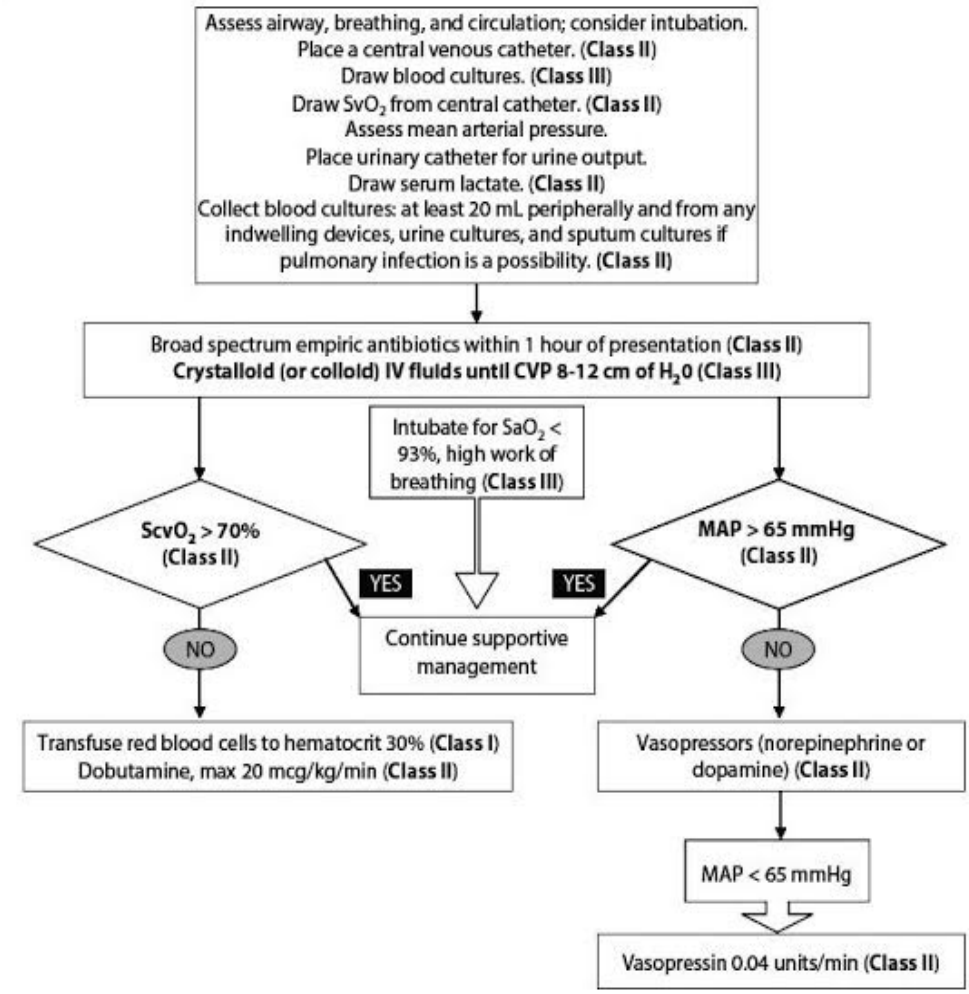
INITIAL RESUSCITATION

Adequate IV fluids have to be infused to maintain targets of

1. Central venous pressure 8-12 mm Hg
2. Mean arterial pressure > 65 mm Hg
3. Venous oxygen saturation > 70 %
4. Urine output > 0.5 ml / kg / hr
5. Normalisation of lactate levels

The ideal fluids for the initial resuscitation are crystalloids. With caution, an initial fluid challenge of about 15 – 30 ml / kg to be given. Further fluids are infused based on the hydration status , vitals and urine output. Vasopressors and inotropes are considered when the blood pressure fails to pick up despite adequate fluid resuscitation. Blood products are given if hemoglobin concentration less than 7 gm %. A platelet count of < 10,000 per cu mm necessitates platelet transfusion. If surgery is planned a higher platelet count of around 50,000 / cu mm is maintained to avoid complications.

The algorithm for the initial resuscitation in a case of severe sepsis is shown in the following picture.



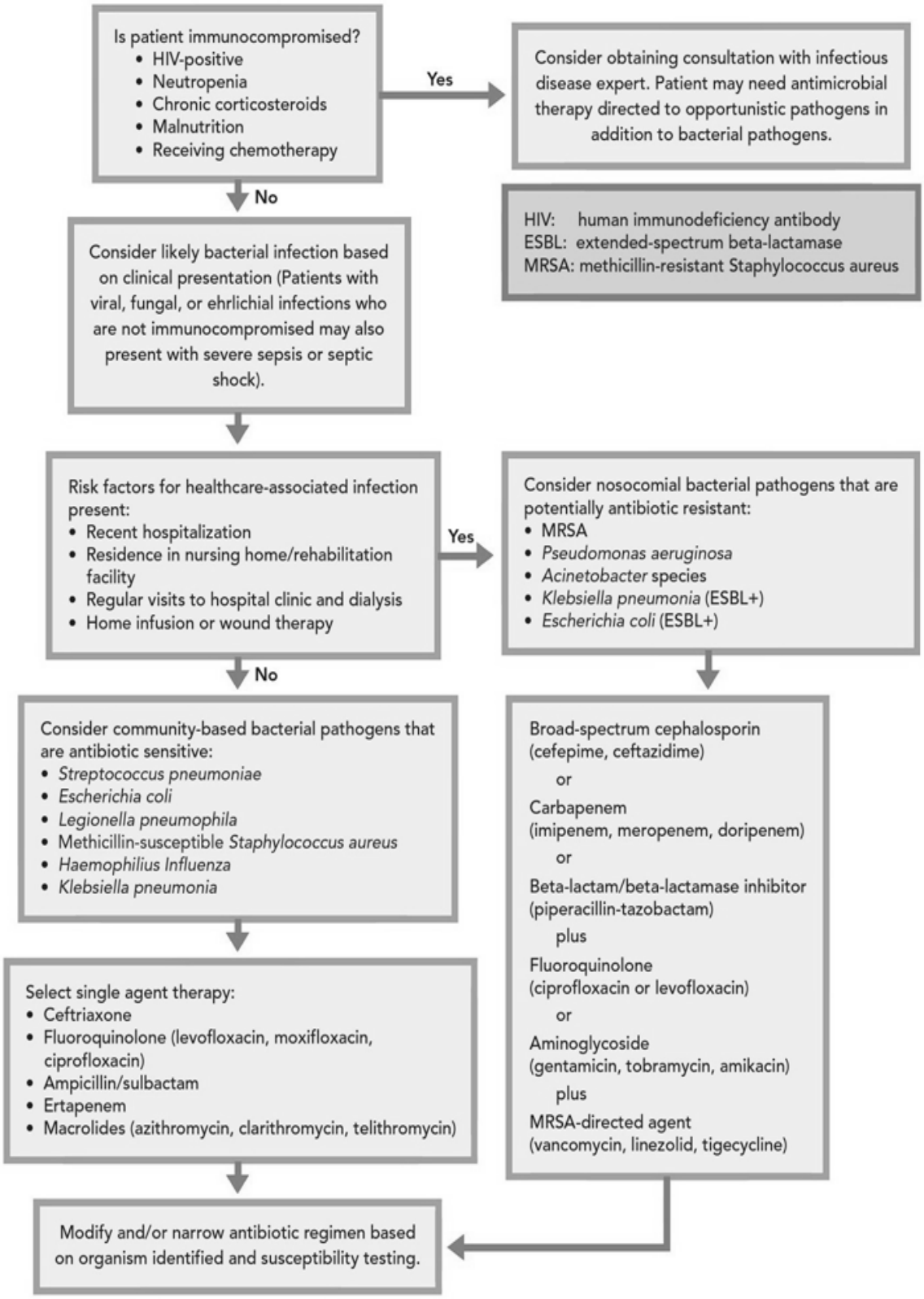
NUTRITIONAL SUPPORT

Adequate calories must be given according to the body weight of the patient. Preferred choice is the enteral route.

ANTI BIOTICS

Combination of empirical agents are used especially in immuno compromised and neutropenic patients. After obtaining culture and sensitivity reports empirical therapy is withdrawn. Classically these antibiotics are given for a period of 7 – 14 days.

AN ALGORITHM FOR ANTIBIOTIC PROTOCOL IN SEPSIS



SOURCE CONTROL

The source of infection should be detected at first and necessary steps to be taken to eliminate it. Surgical removal of the infected tissues and fluids are to be considered if it is a closed space infection. Long standing indwelling vascular and other catheters are to be removed appropriately.

The doses and effects of drugs used in the management of severe sepsis are mentioned in the following table.

I. Vasopressors		CO	MAP	SVR
Norepinephrine	0.05–0.5 μg/kg/min	–/+	++	+++
Dopamine	5–20 μg/kg/min	++	+	++
Epinephrine	0.05–2 μg/kg/min	++	++	+++
Phenylephrine	2–10 μg/kg/min	0	++	+++
Vasopressin	0.04 units/min	0	+++	+++
II. Inotrope				
Dobutamine	2.5–10 μg/kg/min	+++	–/+	–/0
III. Drotrecogin alfa (activated)	24 μg/kg/hr for 96 hr			
IV. Corticosteroids				
Hydrocortisone (+/– fludrocortisone 50 μg daily)	50 mg every 6 hr			

Key : CO-cardiac output , MAP – mean arterial pressure , SVR – systemic venous return

ROLE OF STEROIDS

Parenteral hydro cortisone can be given for severe sepsis with shock that is unresponsive to intra venous fluids and vasopressors.

MANAGEMENT OF ARDS

Ideally ARDS to be managed with mechanical ventilation with following parametrs in mind

1. A low tidal volume of around 6 ml / kg is preferred
2. Plateau airway pressures should be < 30 cm H_2O
3. Higher PEEP is to be used to prevent alveolar collapse
4. Recruitment manoeuvres and prone positioning have been reported to have improved outcomes in studies

GLYCEMIC STATUS

An optimal glycemic status , targetting a sugar level of < 180 mg / dl is essential for a better control of sepsis

DIALYSIS

Most patients with severe sepsis are prone to develop acute kidney injury. Renal replacement therapy may be essential in those patients going for renal failure.

DVT PROPHYLAXIS

As the patients with severe sepsis, who are on prolonged bed ridden state, should be given daily small dose of low molecular weight heparin to prevent the formation of deep venous thrombosis (DVT). For patients with a creatinine clearance of < 30 ml/min it should be used cautiously. Patients having hypersensitivity to heparin, alternative choices like compression stockings , intermittent pneumatic compression devices etc can be tried.

STRESS ULCER PREVENTION

Patients suffering from severe sepsis and MODS should be given prophylaxis to prevent from stress ulcers especially in those having a tendency to bleed. The proton pump inhibitors like pantoprazole are the drug of choice, than histamine receptor blockers.

MONITORING THE ORGAN FUNCTION

The organ function parameters are to be monitored throughout the course of treatment. It gives an idea regarding the severity of sepsis and also about the dose tapering and changing of medications. The following chart depicts the variables to be monitored during management

Organ system	Parameter
Respiratory system	PaO2/FiO2 ratio
Renal system	Urine output and serum creatinine
Hematologic system	Platelet count
Central nervous system	Glasgow coma score
Hepatobiliary system	Serum bilirubin and liver enzymes
Cardiovascular system	Blood pressure, arterial lactate
Gastrointestinal system	Gastric intramucosal pH (pHi), ileus, blood in nasogastric aspirate

RISK PROGNOSTICATION IN SEPSIS

Number of scoring systems have been formulated to predict the severity , prognosis and assessment of in-hospital mortality in critically ill patients including those affected from severe sepsis. These systems provide information related to the degree of functional alterationa in various organs and the possibility of serious morbidity and mortality. They generally have two parts – a score and a mortality assessment depending upon the score. The parameters considered are age, comorbid illness if any, functional alterations of organs , use of interventions and admission diagnosis. These prognostic scores are helping the physicians and hospital administrators to improve their decision making skills. They are useful in better utilisation of hospital resources.

Few of those scores are

1. APACHE II { Acute Physiology and Chronic Health Evaluation } Score
2. SAPS { Simplified Acute Physiology } Score
3. SOFA {Sequential or sepsis related Organ Failure Assessment } Score
4. MPM { Mortality Prediction Model}

Based on the evalution of these scoring systems, they are categorised into generations as shown below

First generation:	Second generation
APACHE I	APACHE II
	SAPS I
	MPM I
Third generation	Fourth generation
APACHE III	APACHE IV
SAPS II	SAPS III
MPM II	MPM_0 III

In general those data that are objective, highly reproducible and easy to measure are used in the scoring systems. Depending on these data and associated equations the risk scores are calculated and the patients may be classified into varying levels of risk groups.

REQUISITES FOR A GOOD PROGNOSTIC SCORING SYSTEM

A scoring system can be considered as best, if it satisfy the following points like

- Simple
- Easy to use
- Universally applicable
- Reliable and consistent
- Good sensitivity and specificity

Among the various scoring systems that are used in the critically ill patients , the two systems that have been verified in many studies and shown to be effective prognosticatory tools, are the APACHE II and SOFA scores.

APACHE II SCORE

The APACHE II or the Acute Physiology And Chronic Health Evaluation Score was first formulated by the US researchers led by Knaus et al. This model has been upgraded three times following British and Irish studies and thus APACHE I , II and III were born. Among these the APACHE II has the benefit scores for age , past comorbid conditions and acute physiological parameters. The following 12 parameters are to be taken within the first 24 hours of presentation

i. Temperature

ii. Mean arterial pressure

iii. Heart rate

iv. Respiratory rate

v. pAO2

vi. arterial pH or serum bicarbonate

vii. serum potassium

viii. serum sodium

ix. serum creatinine

x. hematocrit

xi. white blood cell count

xii. Glasgow coma scale

The following cases in general are not scored using the APACHE II system

- Age of admission < 16 years
- Duration of stay in the ward < 8 hours
- Admission is for primary burns
- Admission following coronary bypass grafting
- If the twelve variables within first 24 hours are not available

The method of calculation of the APACHE II score is shown in the subsequent table.

APACHE II SCORE CALCULATION CHART

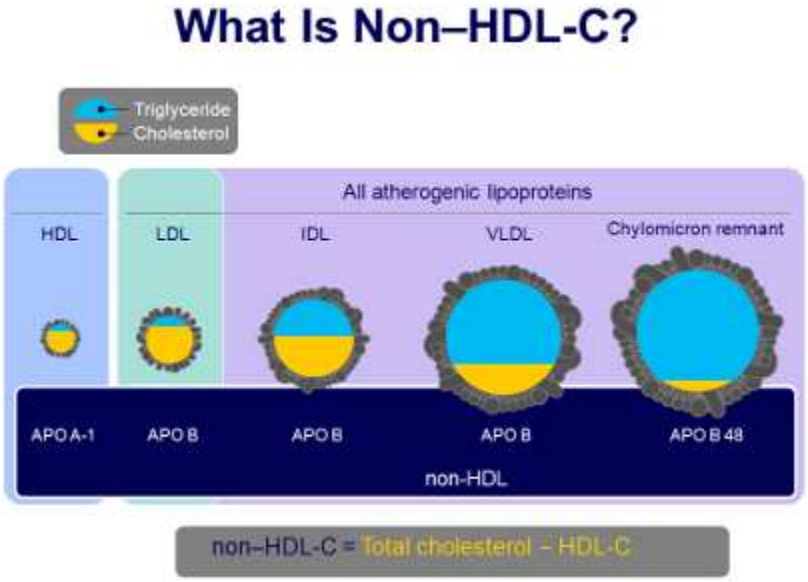
Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

SOFA SCORE

The SOFA or Seqential Organ Failure Assessment score is used to monitor the health status of a critically ill patient. This score is the summation of six different scores , each of which represents an organ system. The organs taken into account for the calculation of SOFA score and the corresponding table has been already dicussed under definitions.

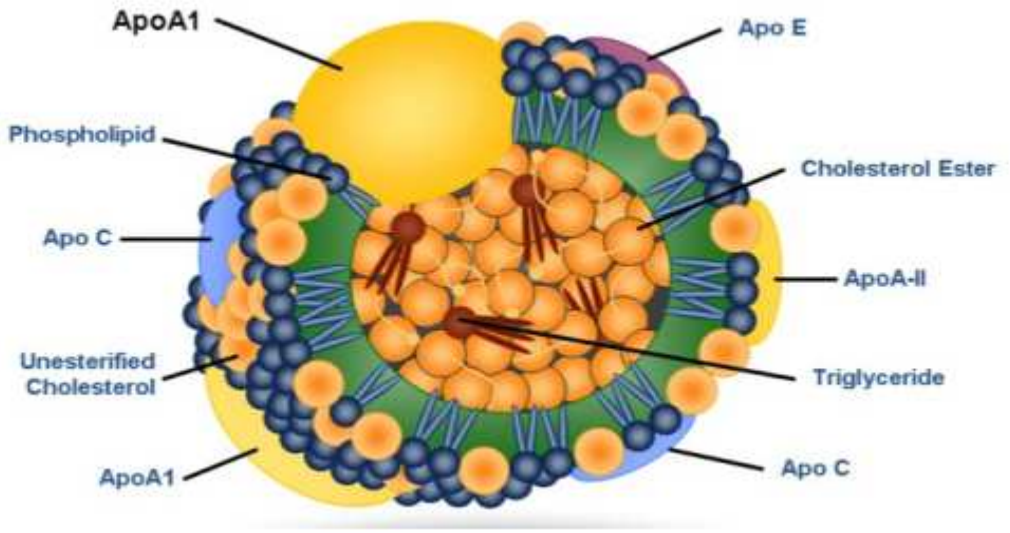
HIGH DENSITY LIPOPROTEINS (HDL):

Lipoproteins are complex molecules composed of number of proteins which transport all fat particles in the body within the water in the extracellular space[13].There are five types of plasma lipoprotein particles namely High density lipoproteins (HDL), Low density lipoproteins(LDL), Intermediate density lipoproteins (IDL), Very low density lipoproteins(VLDL) and Ultra low density lipoproteins(ULDL) commonly called as Chylomicrons and shown below.



HDL contains 80 to 100 proteins per particle and it transports hundreds of fat molecules in each particle. The larger lipoprotein particles carry fat molecules to cells, but HDL scavanges the fat from cells. Higher level of HDL is strongly associated with the decrease in the formation of atherosclerosis[14]. This will reduce the chance of atherosclerotic plaque rupture, sudden myocardial infarction, cerebro vascular accidents and other vascular diseases[15],[16].Hence the name “good cholesterol”.

STRUCTURE OF HDL



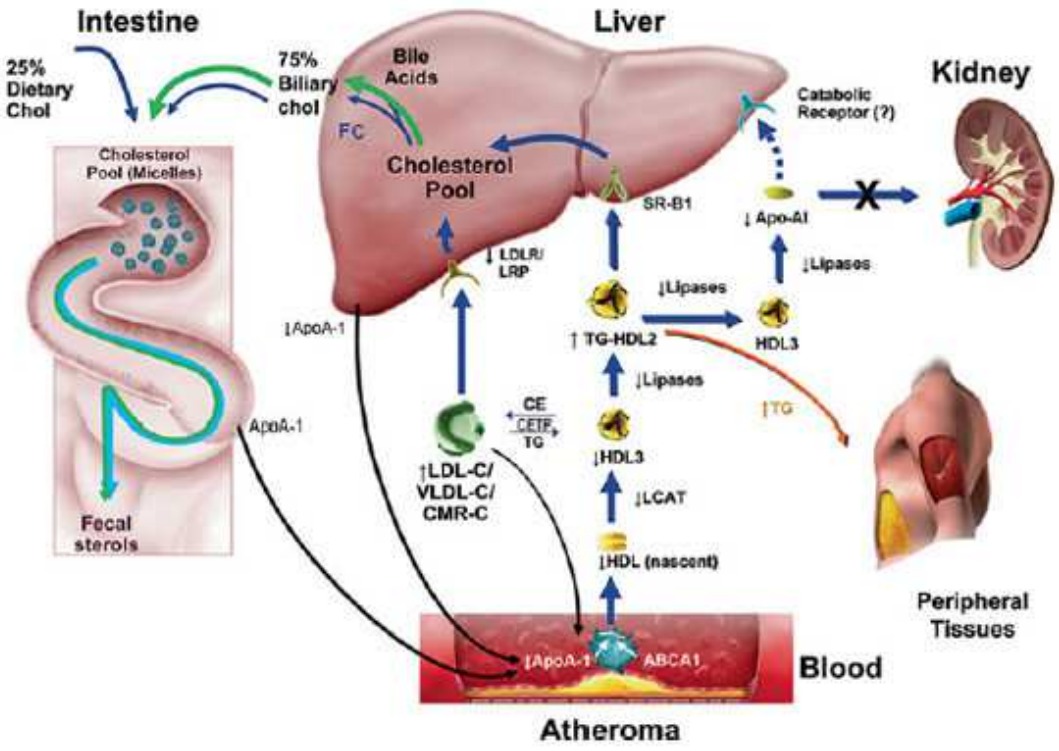
METABOLISM OF HDL

The densest lipoprotein , having high proportion of proteins to lipids. The apolipoproteins like apoA-I and apoA-II are abudantly seen. A rare variant, ApoA-I Milano is more effective in preventing atherosclerosis. The liver synthesizes these lipoproteins as complexes of apolipoproteins and phospholipids. They mimic the cholesterol free flattened spherical lipoprotein particles. These compounds are able to pick up cholesterol, which are carried internally in the cells by binding with the ATP- binding cassette transporter A1(ABCA1)[17]. An enzyme in the plasma called lecithin – cholesterol acyl transferase(LCAT) helps in conversion of free cholesterol to cholesterol esters. This complex then bind with the core lipoprotein molecule and helps in forming the fresh spherical shape HDL.

Then the HDL gains bigger size as they go through the blood stream and acquire more cholesterol and phospholipid particles from cells and rest of the lipoproteins. This action is carried out by the interaction to ABCG1 transporter and the phospholipid transport protein (PLTP).

By the direct and indirect pathways HDL is tranporting cholesterol to liver and the organs like adrenal glands, ovary and testis for the synthesis of steroids. Receptors of HDL like scavenger receptor BI (SR-BI) helps in the selective uptake of cholesterol from HDL. Indirect pathway is most common in human beings carried out by cholesterol ester transfer protein (CETP).

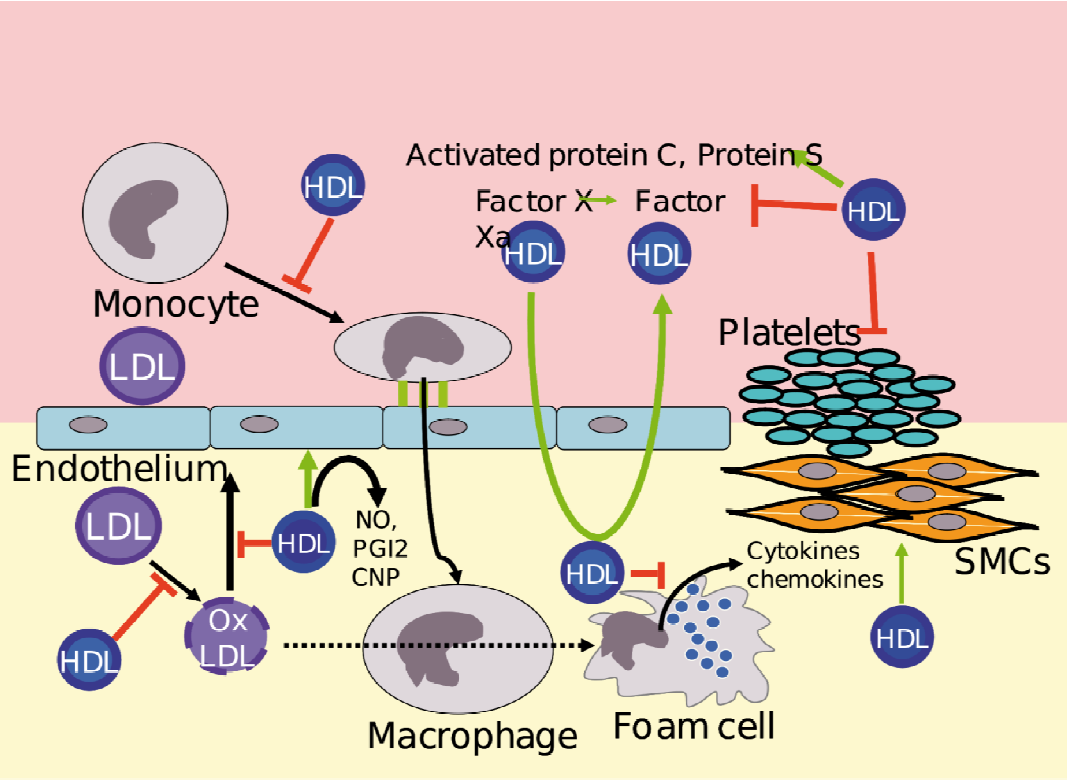
Cholesteryl esters of HDL are exchanged by triglycerides of VLDL, which is carried out by the protein CETP. Because of this reaction VLDLs are transformed to LDL and eventually they are cleared by the LDL receptor pathway. The triglycerides in HDL are unstable, which are degraded by the hepatic lipase and the remaining small HDL molecules will again begin the uptake of cholesterol from cells. HDL metabolism is depicted in the picture shown below.



The cholesterol reaching the liver is excreted through the bile and thus reaching the intestines by directly or indirectly after transforming into bile acids. The uptake of cholesterol from “lipid laden macrophages, termed as foam cells” in the atherosclerotic vessels to the liver and secreted via bile. This is known as “reverse cholesterol transport”, which is the ultimate protective function of HDL against atherosclerosis.

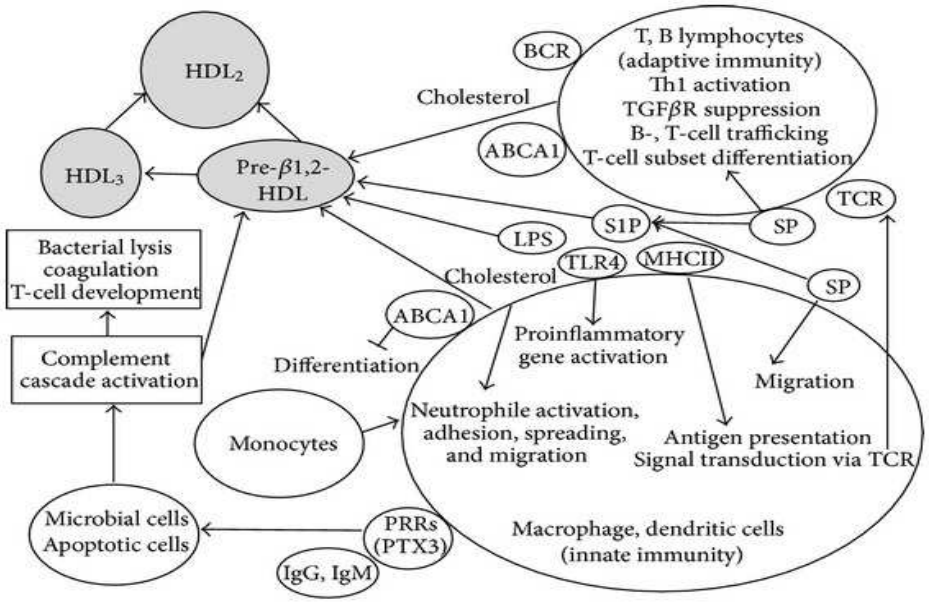
The protein and lipid constituents of HDL are helpful in inhibiting various reactions involved in atherogenesis like oxidation, inflammation, endothelial activation, coagulation and aggregation of platelets. They also

play a role in infections and in chronic inflammatory states.The role of HDL is illustrated in the following picture.

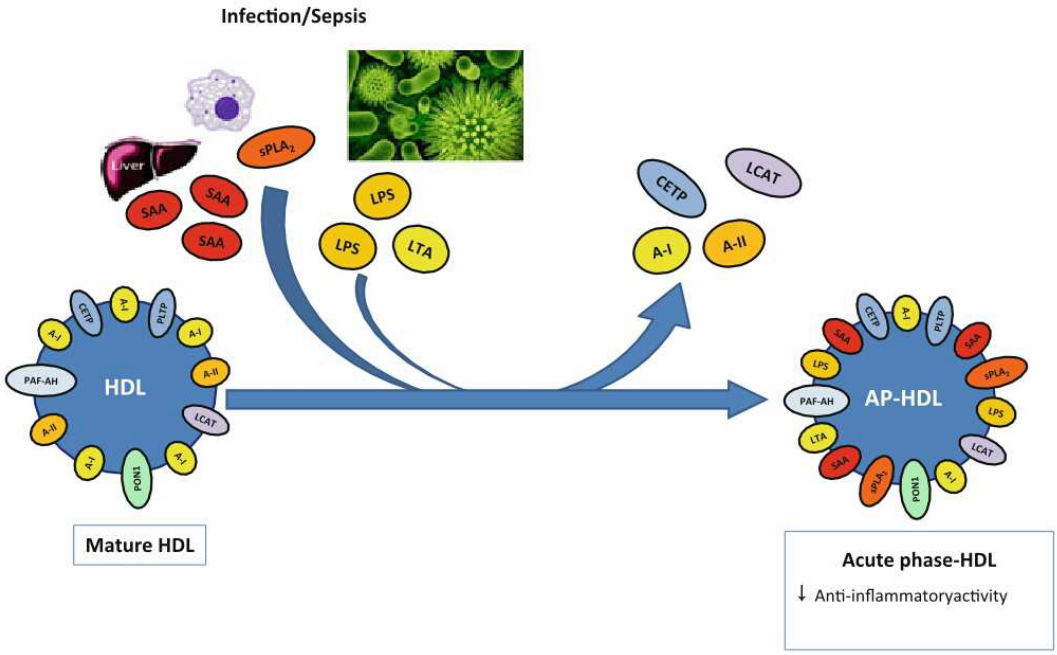


ROLE OF HDL IN INFECTIONS AND SEPSIS

HDL has many important functions in addition to its role in atherosclerosis. Those are proinflammatory, antiinfllammatory and antithrombotic roles , which are depicted in the picture below

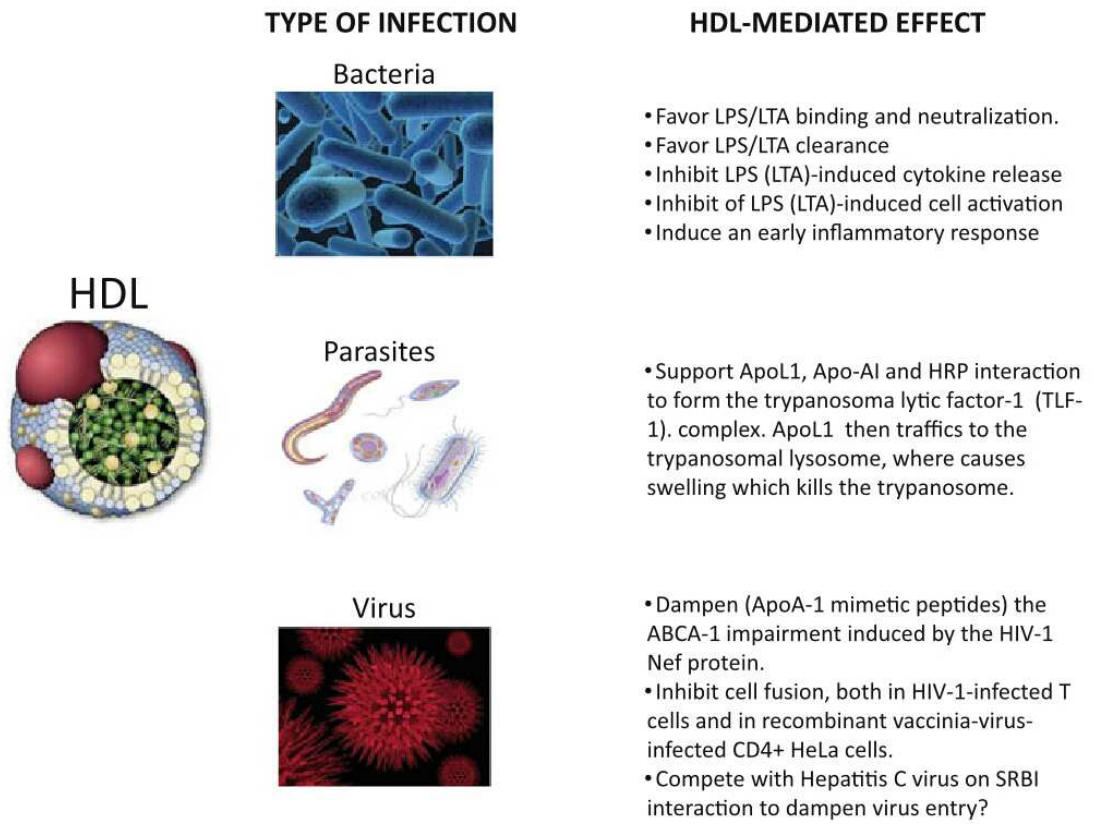


Infections cause reasonable alterations in lipid metabolism and in the composition of lipoproteins[18]. In these situations, there is an increase in the levels of triglycerides and VLDL cholesterol and decrease in levels of HDL and LDL cholesterol[19]. Endotoxin release from infections alters the composition of HDL and size by the reduction of phospholipids and apolipoprotein (apo) A-I, serum amyloid A (SAA) and secretory phospholipase A2 (sPLA2) are grossly increased. Eventhough there is no change in the total particle number, a marked decrease in the number of small and medium size particles is noted. This is shown in the following picture



Low serum levels of HDL is inversely proportional to the severity of sepsis and is related to an extensive systemic inflammatory response. This cholesterol binds with the lipopolysaccharides (LPS) of gram negative organisms and lipoteichoic acid (LTA) of gram positive organisms and neutralises them[20]. Thus help in clearing of those toxins. During parasitic infections, particular component of HDL namely apoL-1, which gives innate immunity against Trypanosomes by causing swelling of lysosomes and thereby killing them[21].

In case of viral infections, there are protein molecules like ABCA1 and SR-BI causing modulation of cholesterol bioavailability in the lipid rafts , which favours the entry of the virus into the cells. The following picture shows the role of HDL in infections



Studies have shown benefits of recombinant HDL and apoA-I adminstrations during infections. Hence serum HDL level measured during infections will help to assess the severity of illness. In the mean time other causes of low HDL to be ruled out. Patients with sepsis, having low HDL level indicates disease severity.Such patients are given intensive medical attention with the anticipation of MODS. Serial monitoring will assist in prognosis and disease outcome.

In this study sepsis patients are selected according to the inclusion and exclusion criteria. On the day of admission, SOFA and APACHE II scores were calculated to assess the severity and serum HDL levels were estimated.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study Centre

Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Govt General Hospital, Chennai

Duration of Study

6 months

Study Design

Descriptional study

Sample Size

100 patients

Inclusion Criteria

Patients of age greater than 18 years with sepsis

Exclusion Criteria

1. Patients on statins
2. Chronic liver disease
3. Chronic kidney disease
4. Thyroid dysfunction
5. Diabetes mellitus

6. Malignancy
7. Chronic inflammatory conditions like Human immuno deficiency virus infection(HIV), Systemic lupus erythematosis(SLE), Rheumatoid arthritis(RA)
8. Patients with malabsorption
9. Pregnancy

Data Collection and Methods

Patients are subjected to history taking , clinical examination and biochemical investigations were done.

Materials and Methods

Patients admitted in medical wards of RGGGH were selected according to the inclusion and exclusion criteria. They were subjected to detailed history taking and physical examination after obtaining proper written consent. Blood samples were collected and sent for biochemical analysis. SOFA and APACHE II scores were calculated on the day of admission. HDL levels were estimated and correlated with SOFA and APACHE II scores.

Procedure / Investigation Details

Serum HDL estimation by enymatic method using fully automated analyser

Analysis Plan

SPSS, Epi INFO softwares

Sponsorship

No

Conflict of interest

None

OBSERVATIONS AND RESULTS

OBSERVATION AND RESULTS

TABLE AND BAR DIAGRAM SHOWING AGE DISTRIBUTION IN THE STUDY SAMPLE

AGE_GROUP

		Frequency	Percent		
Valid	20-30	22	22.0		
	31-40	21	21.0		
	41-50	28	28.0		
	51-60	29	29.0		
	Total	100	100.0		

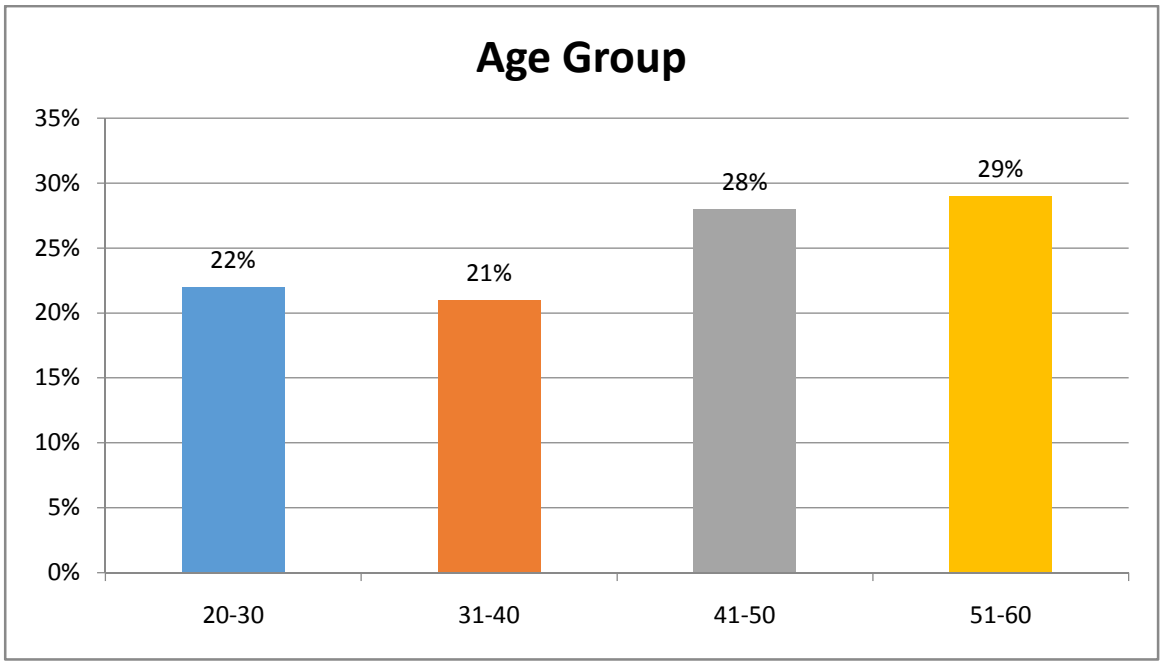


TABLE AND BAR DIAGRAM SHOWING GENDER DISTRIBUTION IN THE STUDY SAMPLE

SEX

		Frequency	Percent		
Valid	MALE	66	66.0		
	FEMALE	34	34.0		
	Total	100	100.0		

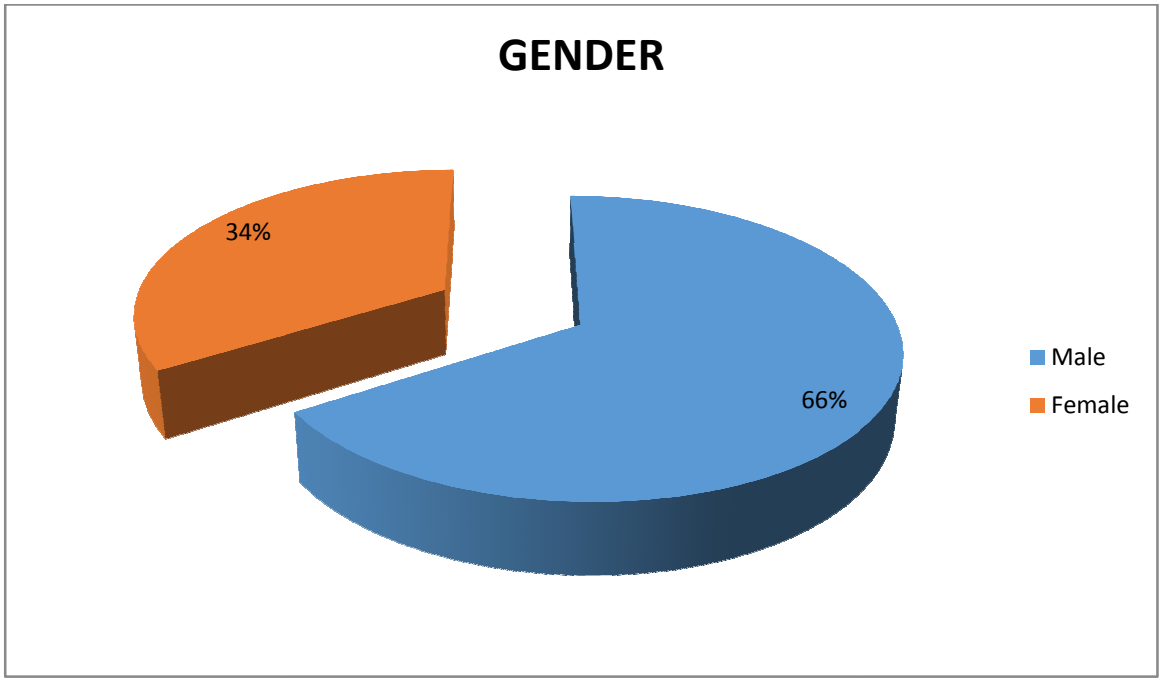
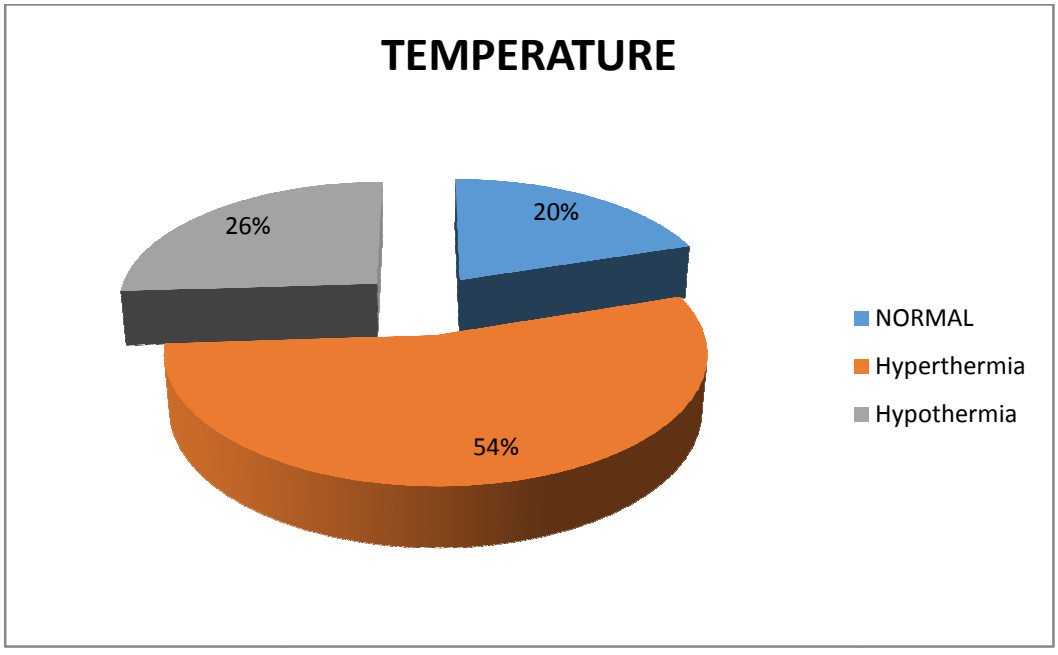


TABLE AND PIE CHART SHOWING DISTRIBUTION OF TEMPERATURE IN THE STUDY SAMPLE

TEMPERATURE

		Frequency	Percent
Valid	NORMAL	20	20.0
	Hyperthermia	54	54.0
	Hypothermia	26	26.0
	Total	100	100.0

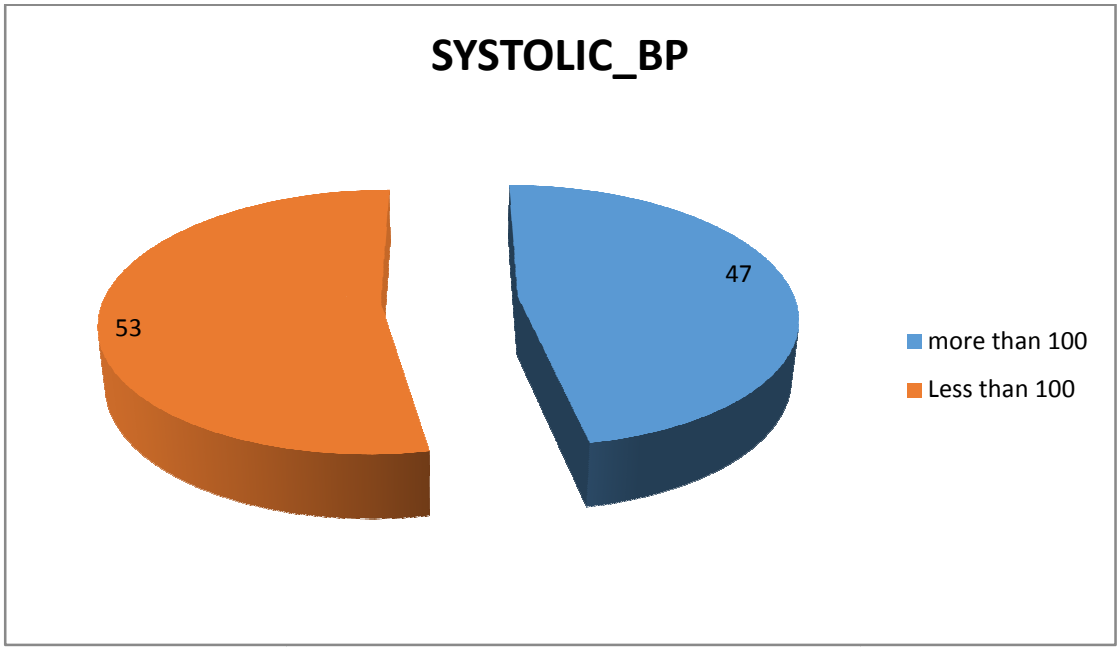


In this study, hyperthermia was observed to be of 54% of study sample.

TABLE AND PIE CHART SHOWING DISTRIBUTION OF SYSTOLIC BP IN STUDY SAMPLE

SYSTOLIC_BP

		Frequency	Percent
Valid	more than 100	47	47.0
	Less than 100	53	53.0
	Total	100	100.0

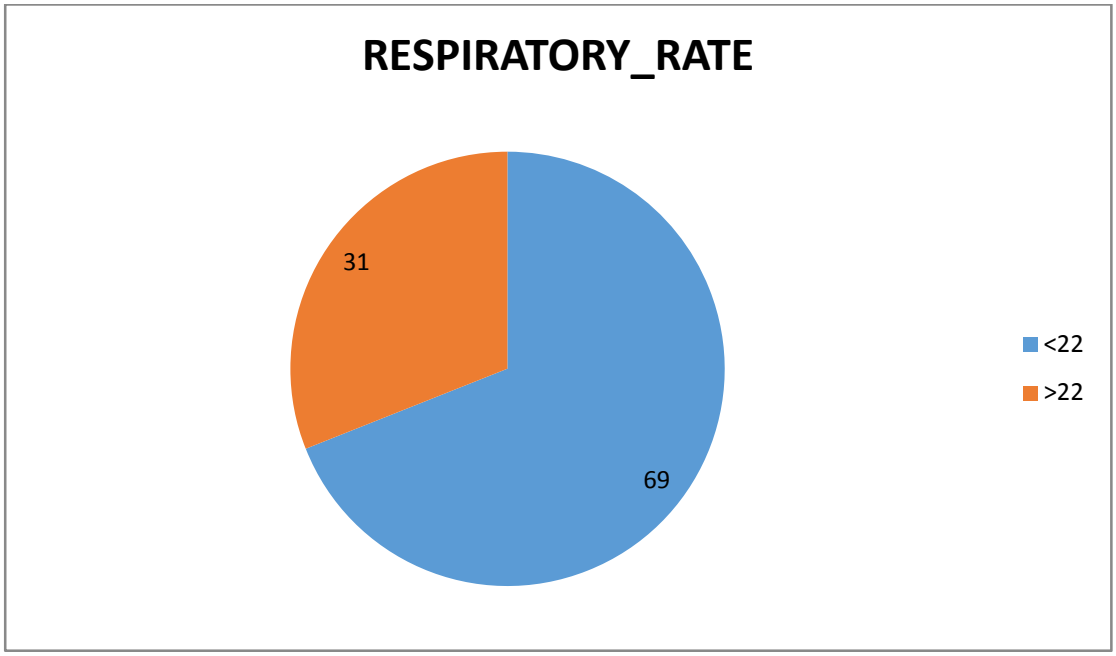


In this study systolic BP less than 100 mmHg was observed in 53% of samples.

TABLE AND PIE CHART SHOWING DISTRIBUTION OF RESPIRATORY RATE IN THE STUDY SAMPLE

RESPIRATORY_RATE

		Frequency	Percent
Valid	<22	69	69.0
	>22	31	31.0
	Total	100	100.0

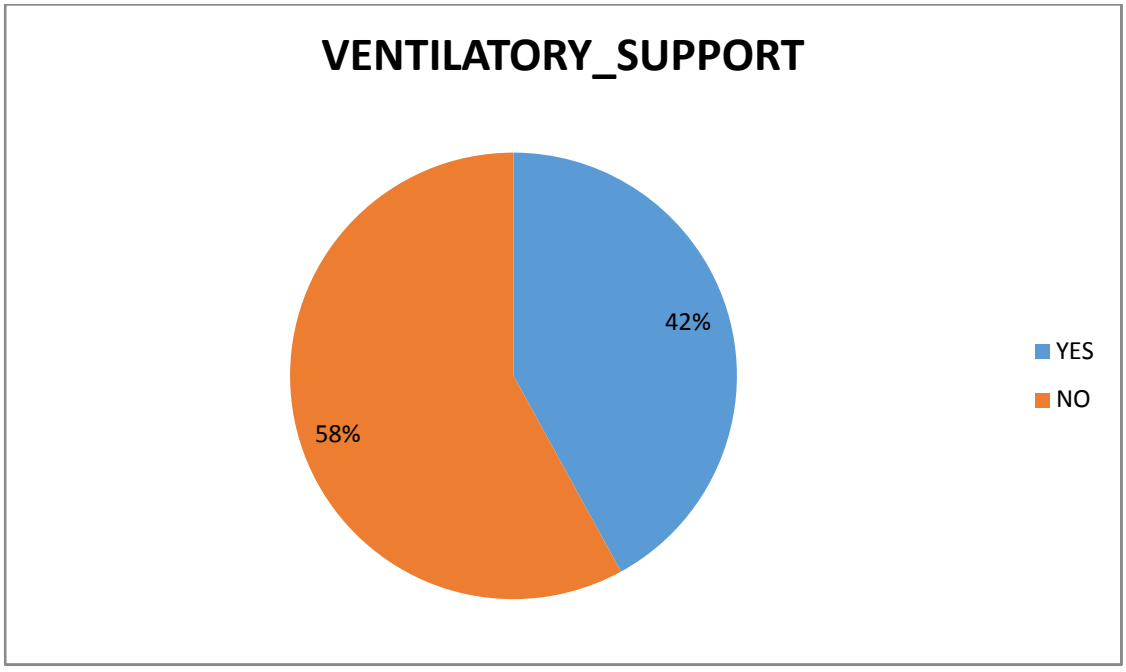


In this study respiratory rate less than 22 was observed in 69% of samples.

TABLE AND PIE CHART SHOWING DISTRIBUTION OF VENTILATORY SUPPORT IN THE STUDY SAMPLE

VENTILATORY_SUPPORT

		Frequency	Percent
Valid	YES	42	42.0
	NO	58	58.0
	Total	100	100.0

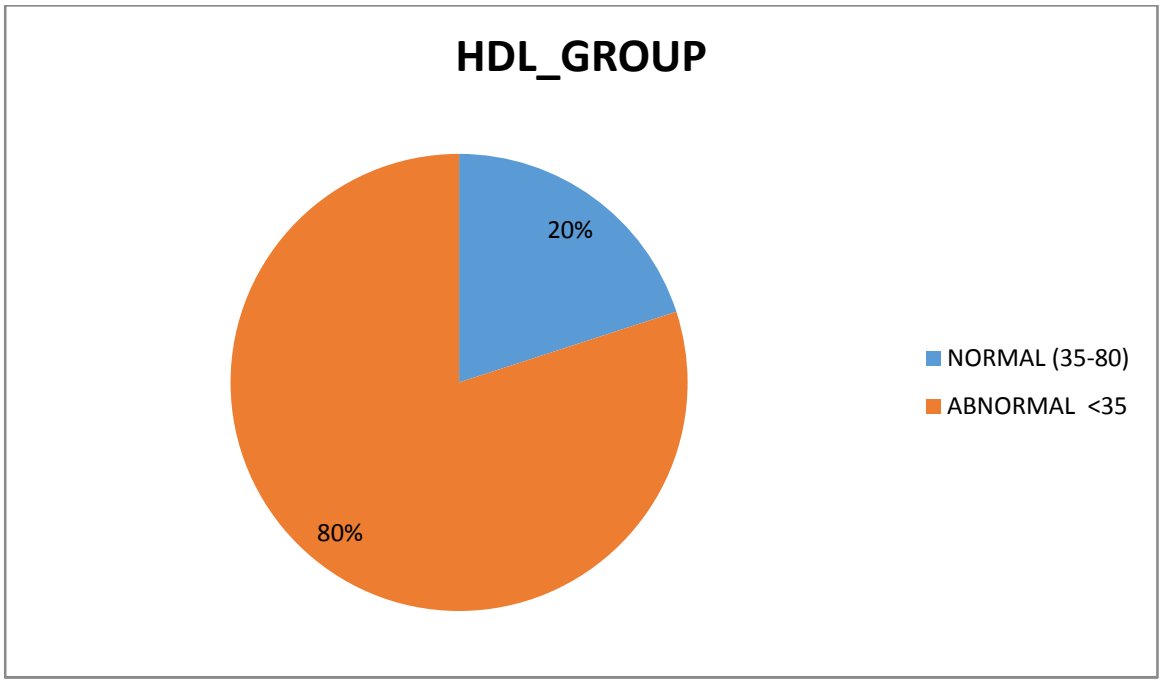


In this study patients without ventilatory support were found to be 58%.

TABLE AND PIE CHART SHOWING DISTRIBUTION OF HDL IN THE STUDY SAMPLE

HDL_GROUP

		Frequency	Percent
Valid	NORMAL (35-80)	20	20.0
	ABNORMAL <35	80	80.0
	Total	100	100.0



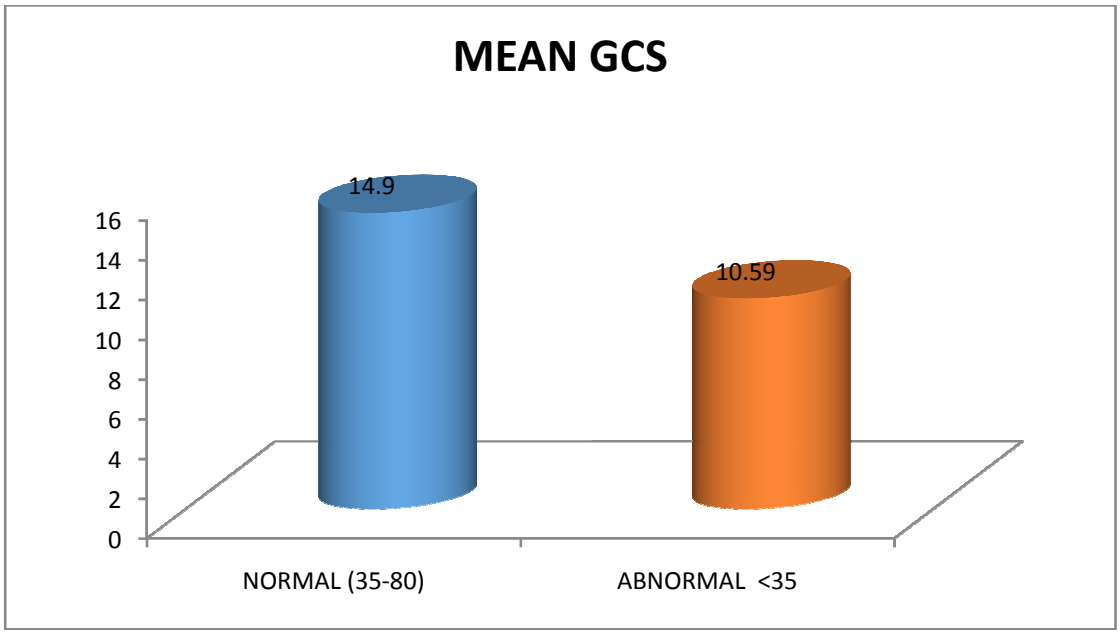
In this study 80% of samples were found to have low HDL levels.

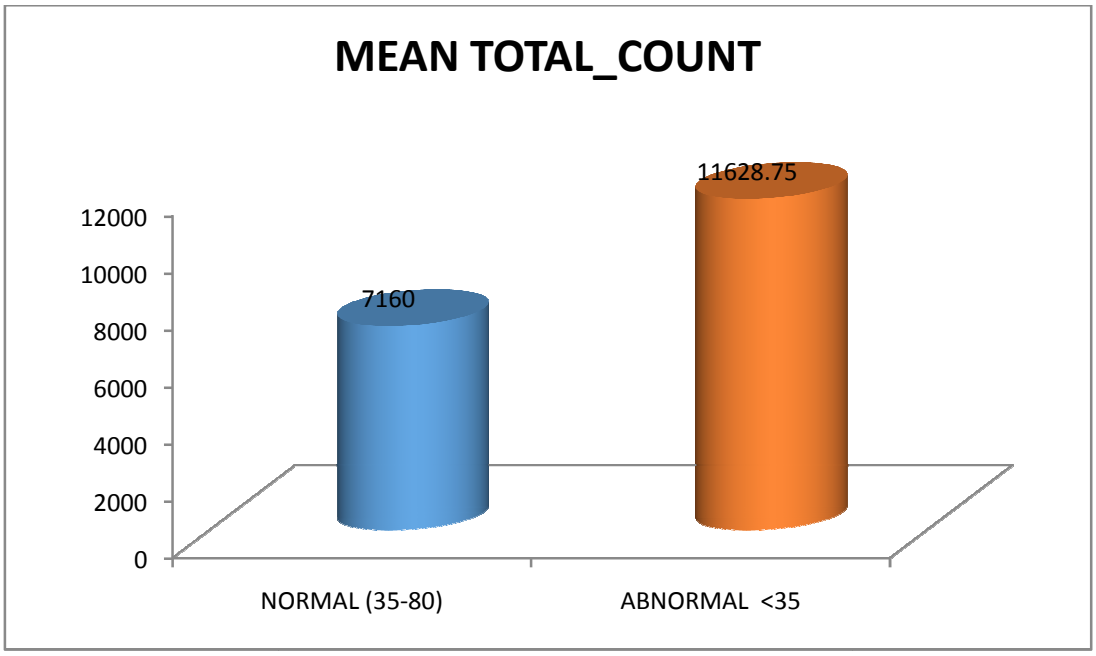
TABLE SHOWING DISTRIBUTION OF GCS, TOTAL COUNT, PLATELET COUNT, BILIRUBIN, CREATININE, APACHE II & SOFA SCORE IN THE STUDY SAMPLE

	HDL_GROUP	N	Mean	Std. Deviation	Std. Error Mean	T VALUE	P VALUE
GCS	NORMAL (35-80)	20	14.90	0.31	0.07	6.524*	P<0.0001
	ABNORMAL <35	80	10.59	2.94	0.33		
TOTAL_COUNT	NORMAL (35-80)	20	7160.00	4701.11	1051.20	2.26*	0.026
	ABNORMAL <35	80	11628.75	8501.50	950.50		
PLATELET_COUNT	NORMAL (35-80)	20	35690.00	20971.43	4689.35	4.123*	P<0.0001
	ABNORMAL <35	80	21175.00	11840.58	1323.82		
BILIRUBIN	NORMAL (35-80)	20	0.95	0.27	0.06	11.202*	P<0.0001
	ABNORMAL <35	80	4.14	2.49	0.28		
CREATININE	NORMAL (35-80)	20	0.98	0.24	0.05	12.191*	P<0.0001
	ABNORMAL <35	80	3.48	1.77	0.20		
APACHE_II_SCORE	NORMAL (35-80)	20	4.15	0.67	0.15	15.985*	P<0.0001
	ABNORMAL <35	80	24.13	11.10	1.24		
SOFA_SCORE	NORMAL (35-80)	20	3.50	0.76	0.17	8.368*	P<0.0001
	ABNORMAL <35	80	13.31	5.21	0.58		

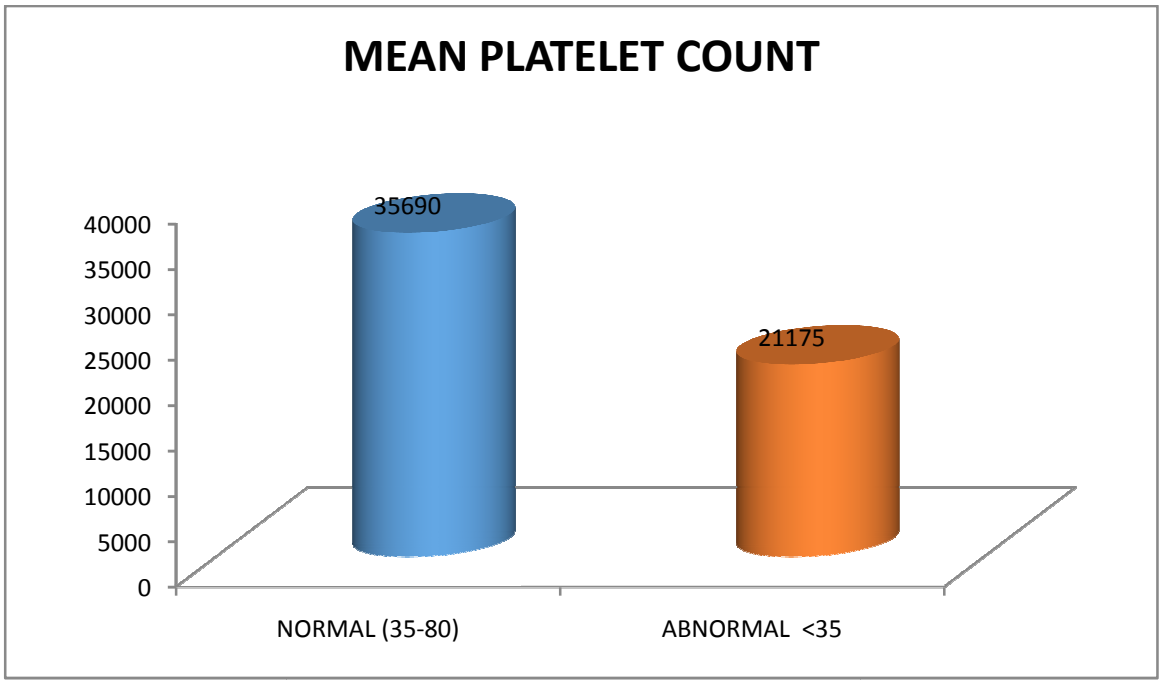
GCS, total count, platelet count, serum bilirubin, serum creatinine, APACHE II and SOFA scores were found to have significant correlation with HDL levels.

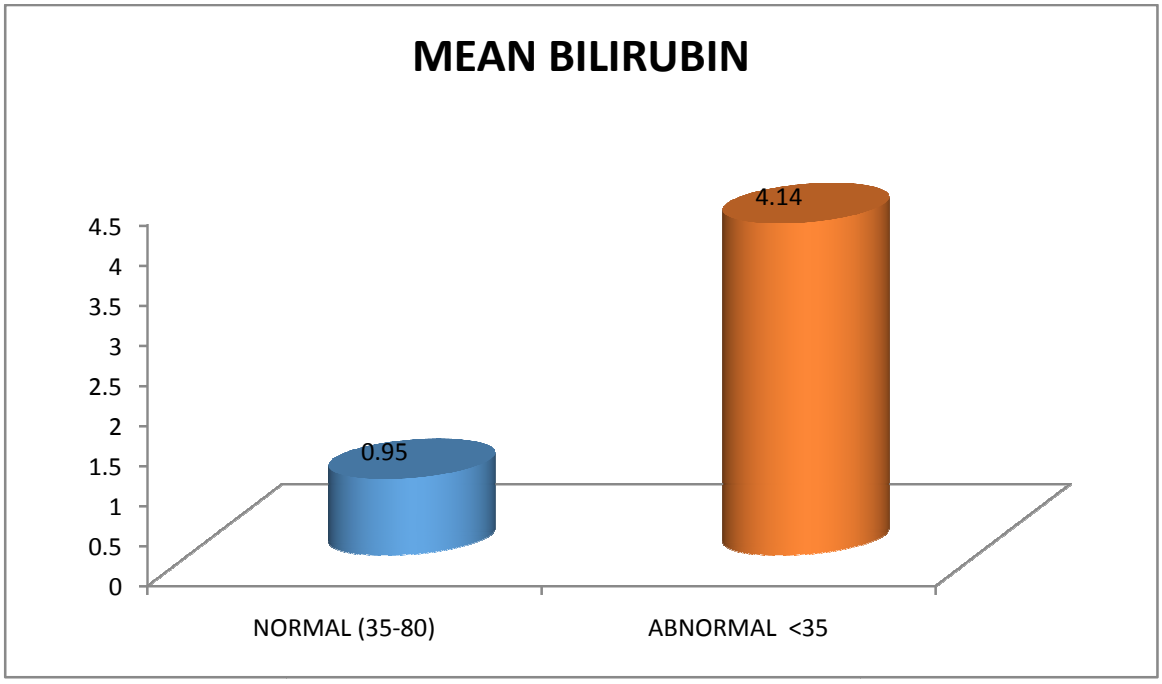
BAR DIAGRAM SHOWING DISTRIBUTION OF GCS AND TOTAL COUNT AMONG HDL NORMAL/ ABNORMAL STUDY POPULATION



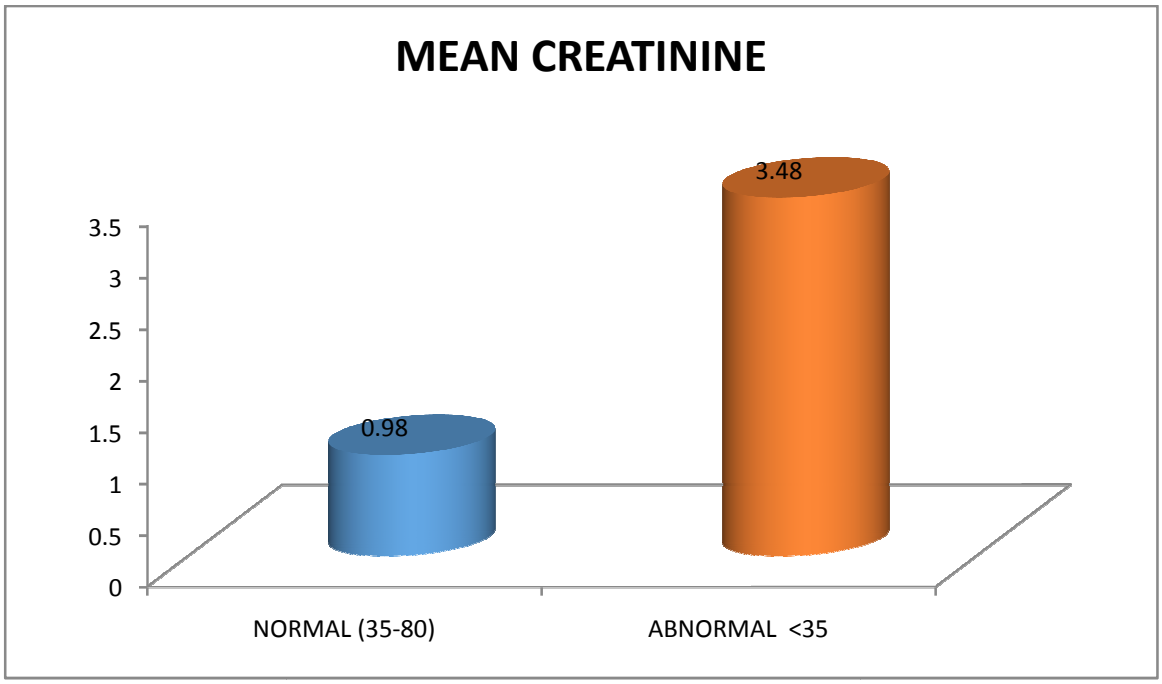


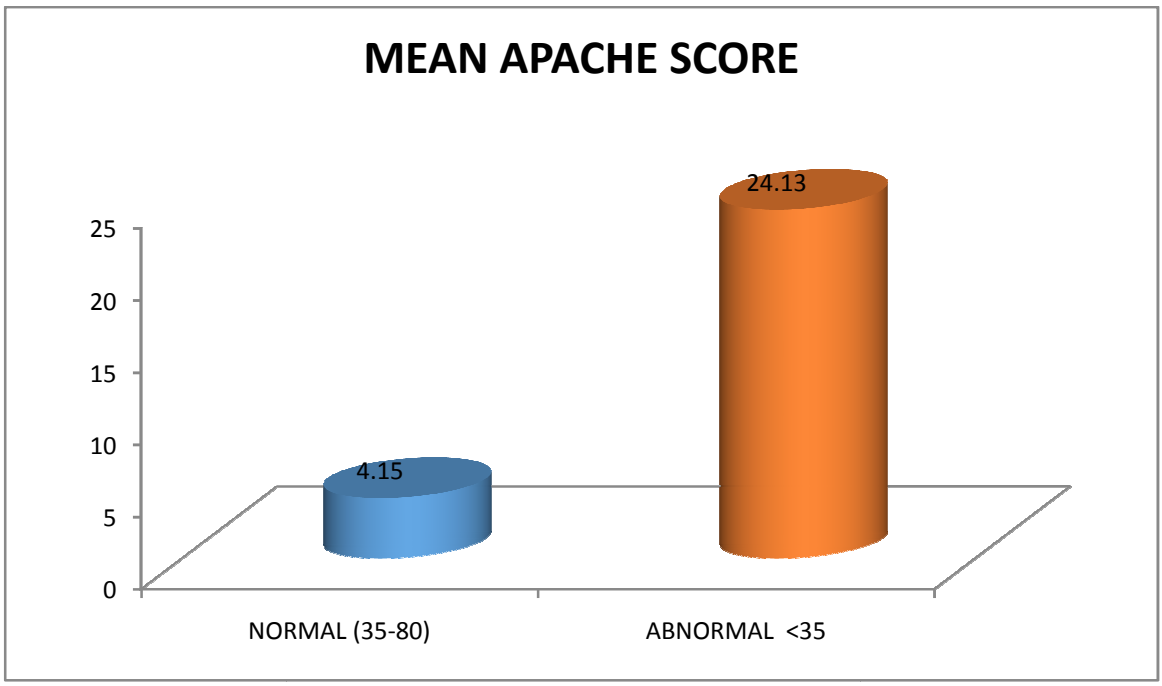
BAR DIAGRAM SHOWING DISTRIBUTION OF PLATELET COUNT & BILIRUBIN AMONG HDL NORMAL / ABNORMAL GROUPS



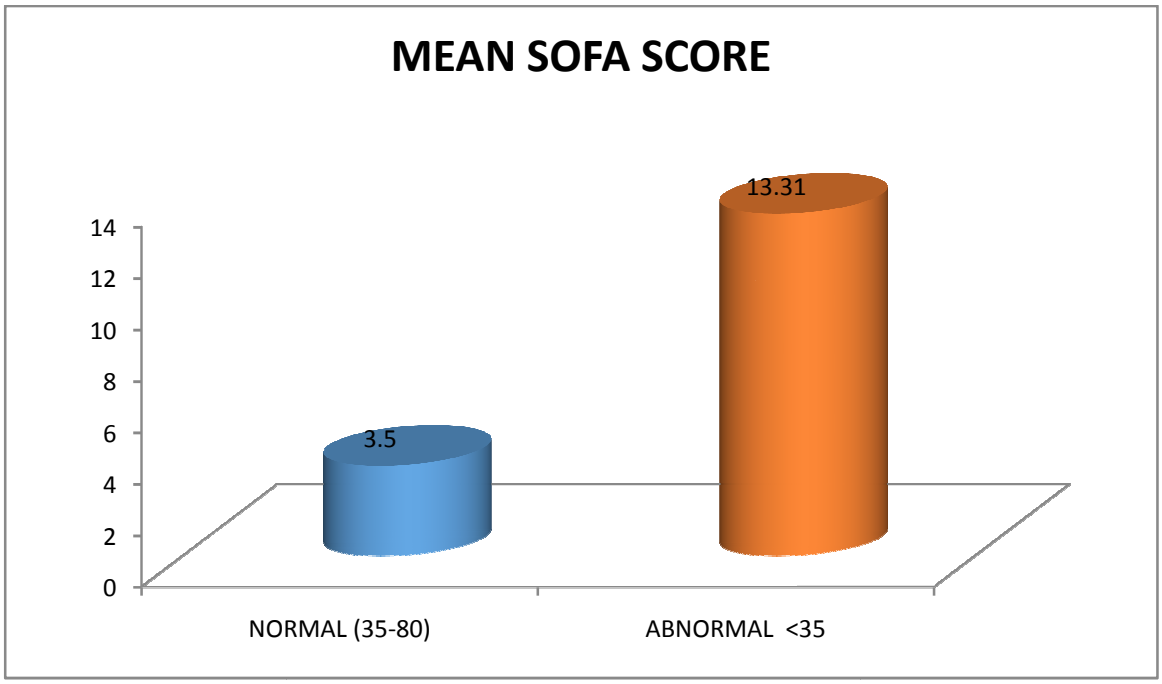


BAR DIAGRAM SHOWING DISTRIBUTION OF CREATININE & APACHE II SCORE AMONG HDL NORMAL / ABNORMAL GROUPS





BAR DIAGRAM COMPARING SOFA SCORE AMONG NORMAL / ABNORMAL HDL GROUP

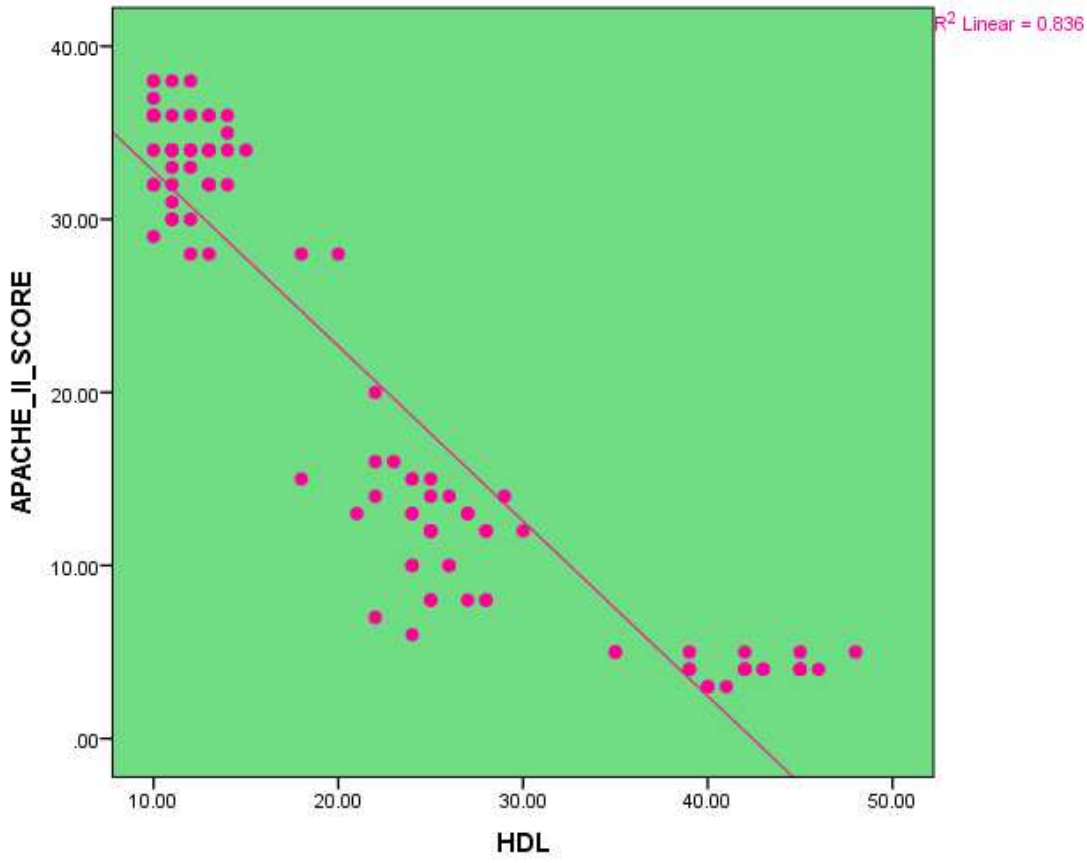


CORRELATIONS		SOFA_SCORE	APACHE_II_SCORE	GCS
HDL	Pearson Correlation	-.916**	-.914**	.830**
	Sig. (2-tailed)	.000	.000	.000
	N	100	100	100

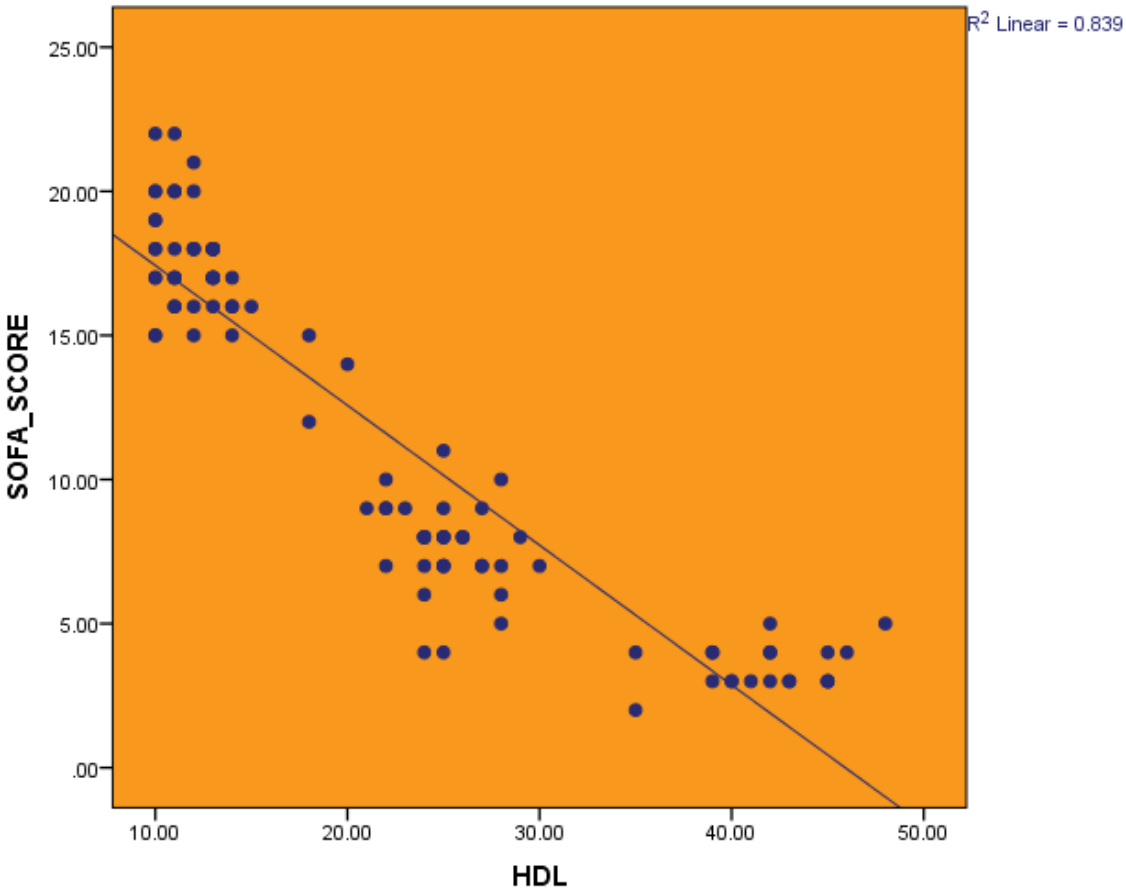
**. Correlation is significant at the 0.01 level (2-tailed).

SOFA and APACHE II scores were having significant correlation with HDL level.

SCATTER DIAGRAM SHOWING CORRELATION BETWEEN APACHE II SCORE AND HDL LEVEL



SCATTER DIAGRAM SHOWING CORRELATION BETWEEN SOFA SCORE AND HDL LEVEL



TABLES SHOWING AGE & GENDER DISTRIBUTION AMONG HDL GROUPS

Crosstab

			AGE_GROUP				Total
			20-30	31-40	41-50	51-60	
HDL_GROUP	NORMAL (35-80)	Count	6	5	2	7	20
		% within HDL_GROUP	30.0%	25.0%	10.0%	35.0%	100.0%
	ABNORMAL <35	Count	16	16	26	22	80
		% within HDL_GROUP	20.0%	20.0%	32.5%	27.5%	100.0%
Total		Count	22	21	28	29	100
		% within HDL_GROUP	22.0%	21.0%	28.0%	29.0%	100.0%

Pearson Chi-Square=4.121 P=0.249

Crosstab

			SEX		Total
			MALE	FEMALE	
HDL_GROUP	NORMAL (35-80)	Count	10	10	20
		% within HDL_GROUP	50.0%	50.0%	100.0%
	ABNORMAL <35	Count	56	24	80
		% within HDL_GROUP	70.0%	30.0%	100.0%
Total		Count	66	34	100
		% within HDL_GROUP	66.0%	34.0%	100.0%

Pearson Chi-Square=2.852 P=0.091

TABLE AND BAR DIAGRAM SHOWING TEMPERATURE DISTRIBUTION AMONG HDL GROUPS

Crosstab

			TEMPERATURE			Total
			NORMAL	Hyperthermia	Hypothermia	
HDL_GROUP	NORMAL (35-80)	Count	10	10	0	20
		% within HDL_GROUP	50.0%	50.0%	0.0%	100.0%
	ABNORMAL <35	Count	10	44	26	80
		% within HDL_GROUP	12.5%	55.0%	32.5%	100.0%
	Total	Count	20	54	26	100
		% within HDL_GROUP	20.0%	54.0%	26.0%	100.0%

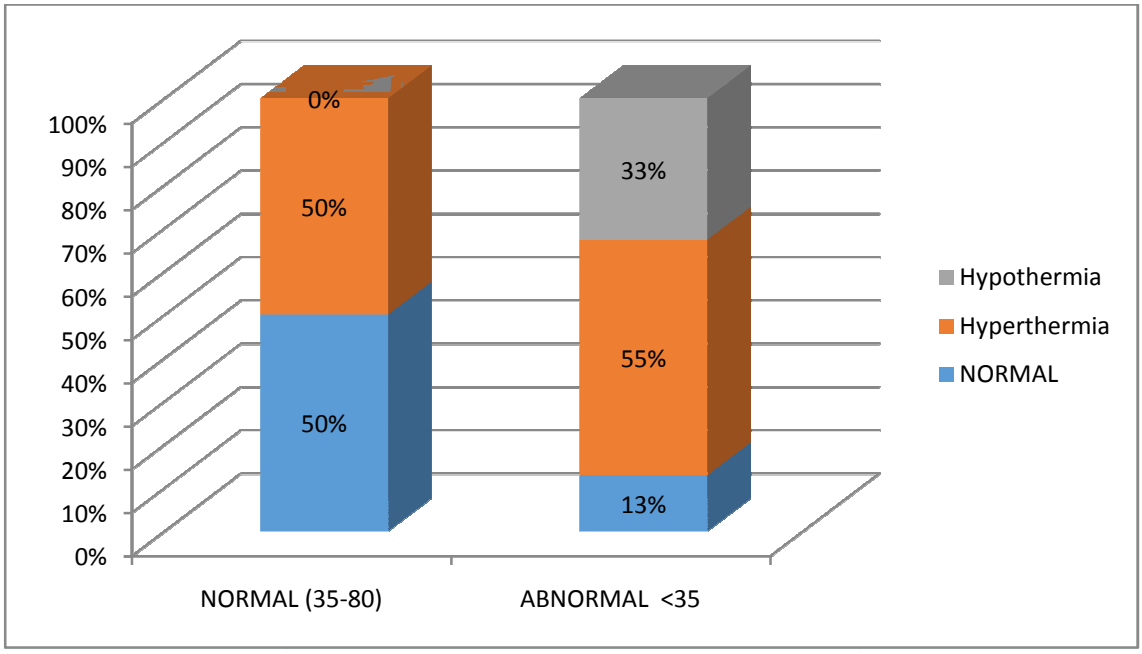


TABLE AND BAR DIAGRAM SHOWING DISTRIBUTION OF SYSTOLIC BP AMONG HDL GROUPS

Crosstab

			SYSTOLIC_BP		Total
			more than 100	Less than 100	
HDL_GROUP	NORMAL (35-80)	Count	19	1	20
		% within HDL_GROUP	95.0%	5.0%	100.0%
	ABNORMAL <35	Count	28	52	80
		% within HDL_GROUP	35.0%	65.0%	100.0%
	Total	Count	47	53	100
		% within HDL_GROUP	47.0%	53.0%	100.0%

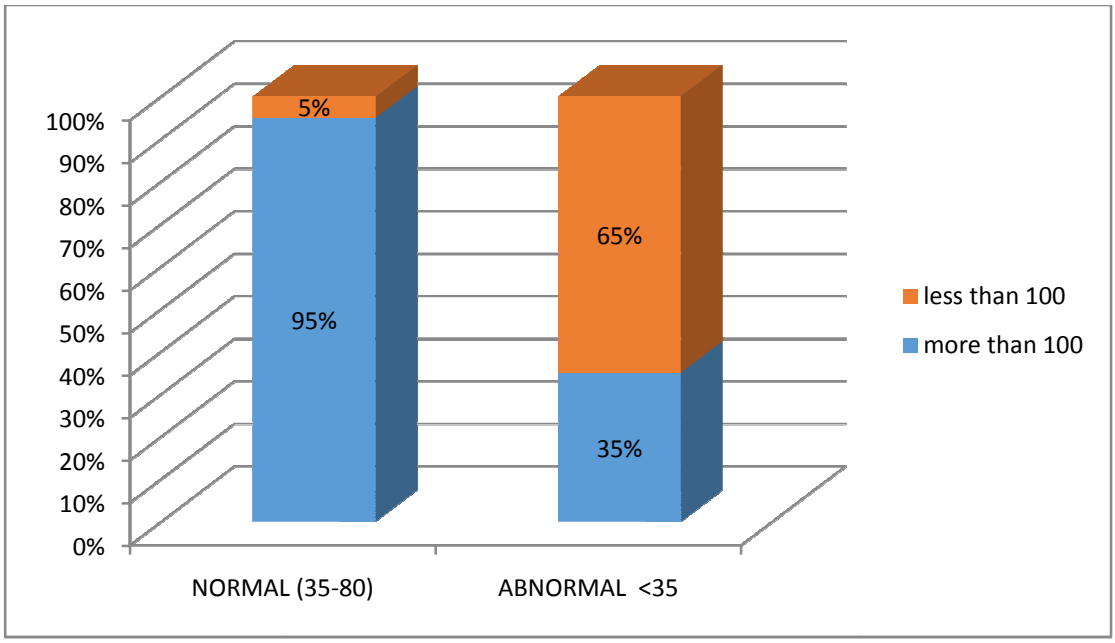
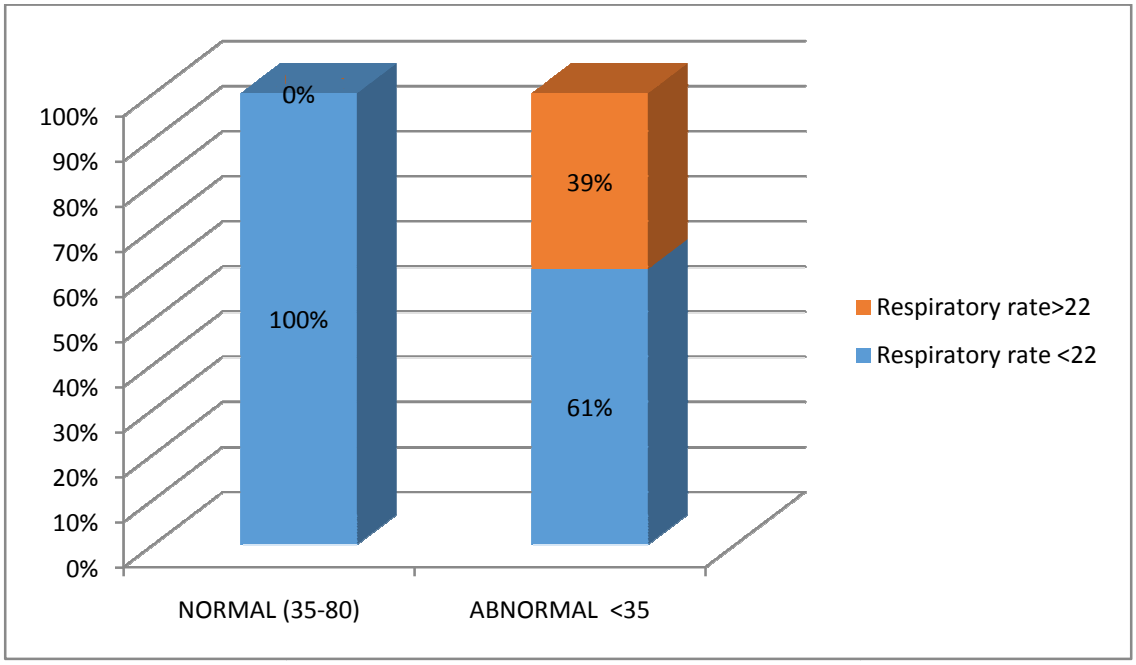


TABLE AND BAR DIAGRAM SHOWING DISTRIBUTION OF RESPIRATORY RATE AMONG HDL GROUPS

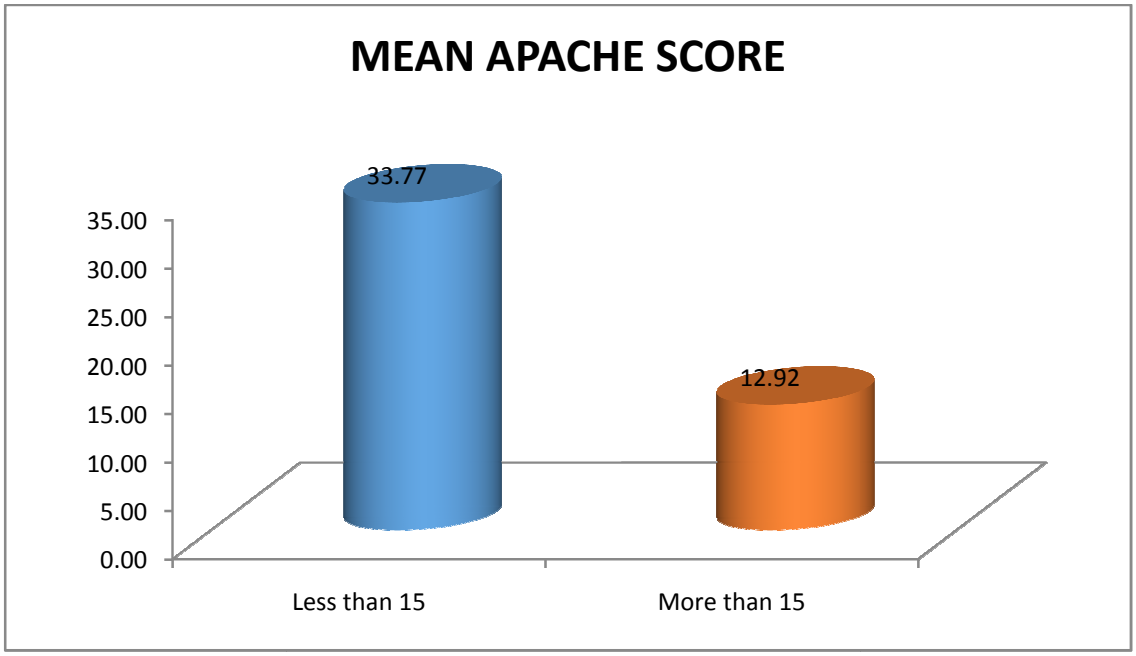
Crosstab

			RESPIRATORY_RATE		Total
			<22	>22	
HDL_GROUP	NORMAL (35-80)	Count	20	0	20
		% within HDL_GROUP	100.0%	0.0%	100.0%
	ABNORMAL <35	Count	49	31	80
		% within HDL_GROUP	61.3%	38.8%	100.0%
Total		Count	69	31	100
		% within HDL_GROUP	69.0%	31.0%	100.0%

Pearson Chi-Square=11.232* P<0.001



BAR DIAGRAM SHOWING APACHE II & SOFA SCORE IN LOW HDL GROUPS



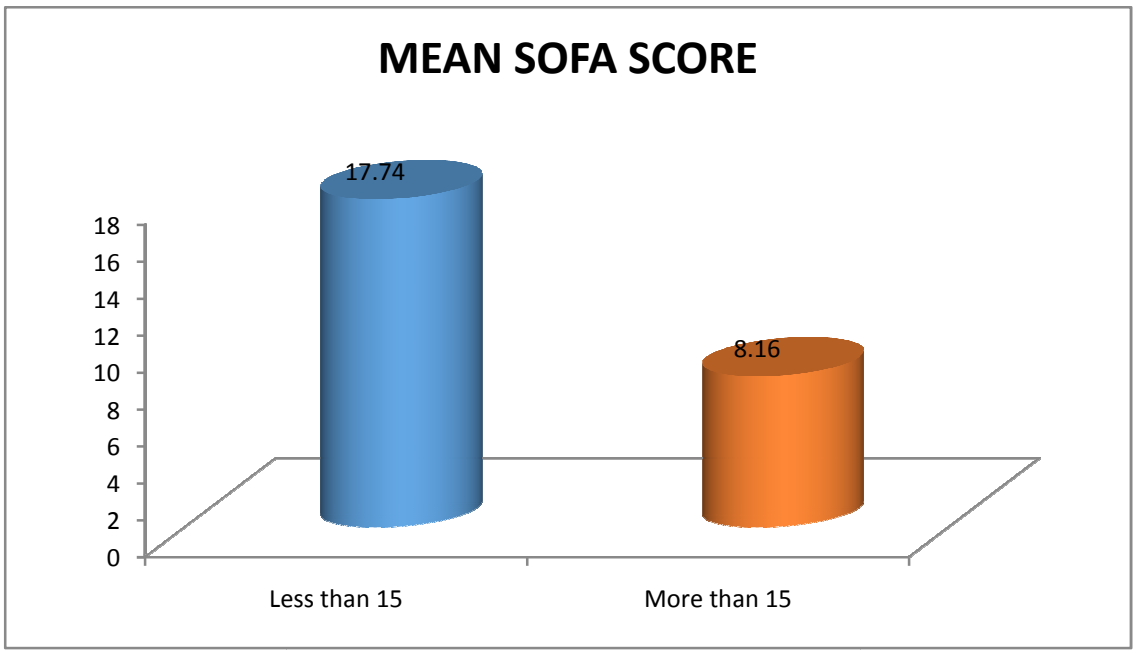


TABLE SHOWING CORRELATION OF SOFA & APACHE II SCORE AMONG LOW HDL GROUPS

Group Statistics FOR 80 ABNORMAL CASES							
	HDL_15	N	Mean	Std. Deviation	Std. Error Mean	T value	P value
APACHE_II_SCORE	Less than 15	43	33.7674	2.63527	.40187		
	More than 15	37	12.9189	4.68673	.77049	24.96*	P<0.001
SOFA_SCORE	Less than 15	43	17.7442	1.81388	.27661	21.123*	P<0.001
	More than 15	37	8.1622	2.24244	.36865		

APACHE II and SOFA scores having significant correlation with low HDL groups.

DISCUSSION

DISCUSSION

This study is an descriptional study done in patients admitted with sepsis. According to the inclusion and exclusion criteria, patients in medical wards of RGGGH were selected. After obtaining proper written consent, they were subjected to detailed history taking and physical examination. Biochemical analysis of collected blood samples were done. SOFA and APACHE II scores were calculated on the day of admission. HDL levels were estimated and correlated with SOFA and APACHE II scores.

In developing countries like India, sepsis remains to be the major cause of mortality and morbidity. Early recognition and prompt treatment will prevent the adverse outcome. SOFA and APACHE II scores help in prognostication of the disease. Serum HDL is one of the widely used investigation in general and is available in most of the centres. The concept of decrease in HDL level in sepsis was used in this study and it has been evaluated. Some of the studies are mentioned below.

A study of serum HDL levels in severe sepsis patients done by Naresh Monigari et al showed significant association of low HDL value on day 1 with mortality[22].

In a study done by Sunil B Kumarasamy et al showed plasma concentrations of HDL were low in severe sepsis patients and reflecting the severity of the disease[23].

A study published by Chien et al showed that low HDL level on day 1of severe sepsis is significantly associated with an increase in mortality and adverse clinical outcome[24].

In this study, serum level of HDL was decreased in 80% of patients. There was a significant correlation between sepsis and HDL level. In our sample, proportion of males got admitted was higher than females. Hyperthermia, systolic BP < 100 mm Hg, respiratory rate < 22/ minute and patients without ventilatory support were in higher proportion.

SOFA and APACHE II scores were inversely proportional with HDL levels. In patients having low HDL levels, these scores were very high and showing poor prognosis. Significant correlation was found between sepsis and HDL and also between HDL and these two scores.

LIMITATIONS OF THE STUDY

A multicentric study with a larger sample size and longer follow up is needed to assess the predictive power of HDL values and the scoring systems such as SOFA and APACHE II.

CONCLUSION

CONCLUSION

Significant correlation was present between the patients with sepsis and serum HDL level. Low HDL values were observed in patients with severe sepsis and in those having severe organ dysfunction.

Higher values of SOFA and APACHE II scores were associated with low HDL levels. HDL level has significant correlation with SOFA and APACHE II scores. In this study HDL level less than 15 mg/dl have higher SOFA and APACHE II scores, indicating poor prognosis in such patients. Hence a simple investigation like HDL can be used as a prognostic marker in sepsis.

Serial monitoring of patients with SOFA score, APACHE II score and HDL values are essential for better than a single value, for better prognostication and best clinical outcome in patients with sepsis.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

NAME : Age/Sex :
IP No : Address :
Patient ID No : Occupation :
Symptoms:
Fever
Cough/burning micturition/loose stools/vomiting/abdominal pain/seizures/skin /soft tissue infections

Past History: Chronic renal disease
Chronic liver disease
Malignancy
Immunosuppressive drugs
DM/ SHT

Pregnancy: yes/no

General examination:

GCS:

Pallor/icterus/cyanosis/clubbing/pedal edema/gen lymphadenopathy

VITALS:

BP:

PR:

RR:

Temp:

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATION:

COMPLETE HEMOGRAM

RENAL FUNCTION TEST

LIVER FUNCTION TEST

URINE ROUTINE

CHEST X-RAY

ELECTROCARDIOGRAM

ULTRASOUND

SERUM HDL

BLOOD/URINE CULTURE

OTHERS

APACHE II SCORE CARD

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:

- 5 points for nonoperative or emergency postoperative patients
- 2 points for elective postoperative patients

SOFA SCORE CARD

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	≤300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Total score -

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.D.Shilpa
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.D.Shilpa,

The Institutional Ethics Committee has considered your request and approved your study titled **"STUDY OF SERUM HDL AS A PROGNOSTIC MARKER IN SEPSIS "** - **NO.(II) 11032016.**

The following members of Ethics Committee were present in the meeting hold on **22.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
5.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

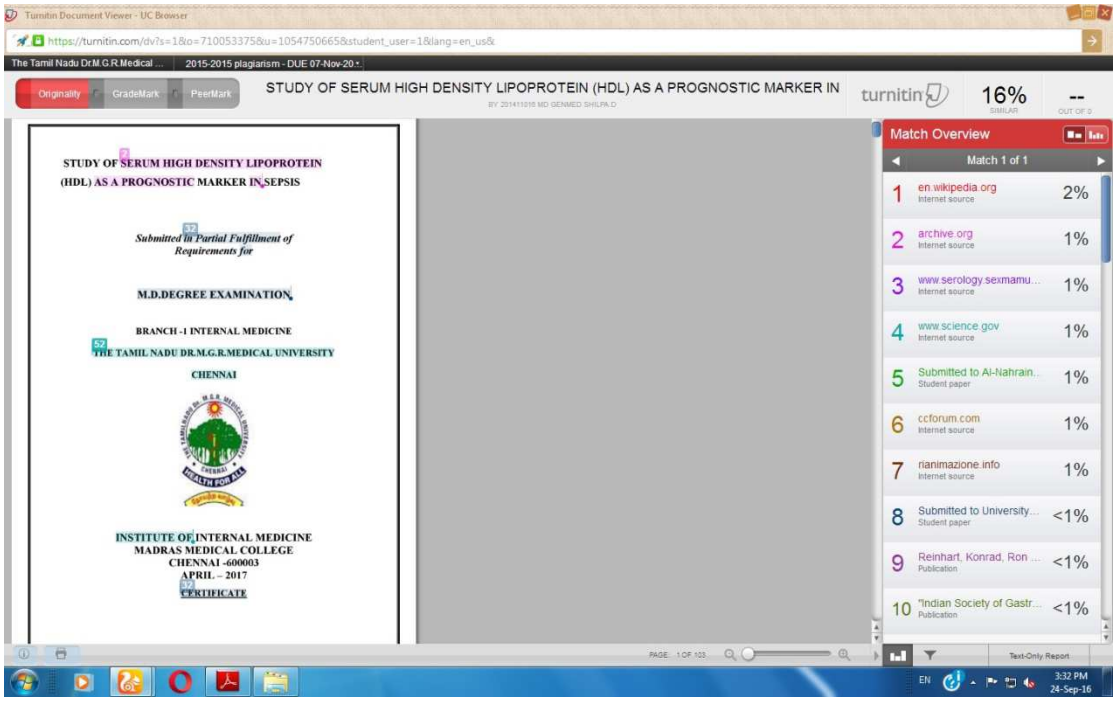
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

MADRAS MEDICAL COLLEGE
31 MAR 2016
CHENNAI-600 003

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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Submitted in Partial Fulfillment of
Requirements for
M.D.DEGREE EXAMINATION,
BRANCH -I INTERNAL MEDICINE
THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI
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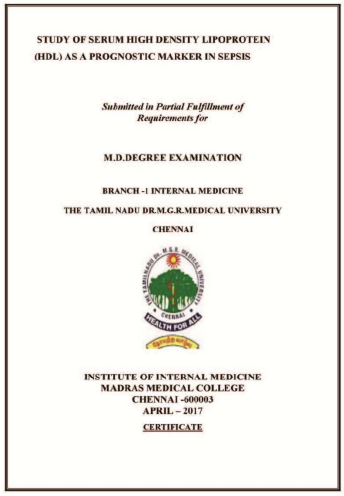

STUDY OF SERUM HIGH DENSITY LIPOPROTEIN
(HDL) AS A PROGNOSTIC MARKER IN SEPSIS

Submitted in Partial Fulfillment of Requirements for

M.D.DEGREE EXAMINATION

BRANCH -I INTERNAL MEDICINE

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

INSTITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI -600003
APRIL – 2017

CERTIFICATE

INFORMATION SHEET

We are conducting a study on **"STUDY OF SERUM HDL AS A PROGNOSTIC MARKER IN SEPSIS"** among patients admitted in Medical ward at the Government General Hospital, Chennai and for that your sample may be valuable to us.

- The purpose of this study is to correlate serum HDL level in sepsis as a prognostic marker among patients admitted in medical ward.
- We are selecting certain cases and if you are found eligible, we may be using your blood sample to perform certain tests, which in anyway do not affect your final report or management.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Signature of participant

Date:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு

சீழ்ப்பிடிப்பு நோயாளிகளின் ஊன்நீரில் உள்ள எச்.டி.எல்(HDL) கொழுப்பின் அளவு நோய்முடிவுமுன்கணிப்பின் அடையாளமாக உள்ளது என்பதை ஆராய்தல்.

ஆய்வு நிலையம் : பொது மருத்துவத்துறை,
சென்னை மருத்தவக் கல்லூரி, சென்னை – 3.

பங்கு பெறுபவரின் பெயர்:
உள்நோயாளி எண்:

பங்குபெறுபவர் இதனை(√)குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும், அந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன் ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த பரிசோதனை முறைகளால் உடலுக்கு எந்தவிதமான உபாதைகளும் இருக்காது என்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் .....இடம்.....தேதி.....
இடது கை பெருவிரல் ரேகை
புங்கேற்பவரின் பெயர் மற்றும் விலாசம்.....
ஆய்வாளரின் கையொப்பம்.....இடம்.....தேதி.....
ஆய்வாளரின் பெயர்.....

PATIENT CONSENT FORM

Study Title		**STUDY OF SERUM HDL AS A PROGNOSTIC MARKER IN SEPSIS**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ☐

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

Study Investigator's Name:

Dr. D.SHILPA

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவத்துறையில் "சீழ்ப்பிடிப்பு நோயாளிகளின் ஊன்நீரில் உள்ள எச்.டி.எல்(HDL) கொழுப்பின் அளவு நோய்முடிவுமுன்கணிப்பின் அடையாளமாக உள்ளது என்பதை ஆராய்தல்" பற்றிய ஆய்வு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை மற்றும் இரத்தப் பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம்:

MASTER CHART

SERIAL.NO	AGE	SEX	TEMPERATURE	SYSTOLIC BP	RESPIRATORY RATE	GCS	TOTAL COUNT	PLATELET COUNT	BILIRUBIN	CREATININE	VENTILATORY SUPPOR	APACHE II SCORE	SOFA SCORE	HDL
1	35	1	1	1	2	12	11000	18000	2.8	1.7	2	15	11	25
2	43	1	0	1	1	13	15000	30000	1.5	2	2	12	10	28
3	38	2	0	1	1	15	9000	80000	1	1.1	2	5	2	35
4	50	2	2	2	2	10	2500	12000	4	3.5	1	32	15	10
5	41	1	1	2	2	9	16500	9000	4.2	6	1	28	18	12
6	22	1	1	2	2	10	18000	11000	5	4.3	2	30	20	11
7	54	1	1	2	1	11	2000	8600	3.4	2.5	1	28	16	13
8	32	2	0	1	1	15	4000	23000	1.4	0.9	2	4	4	45
9	58	2	1	1	2	12	15300	36000	1.5	1.1	2	10	8	26
10	53	1	0	2	2	13	2800	17800	2	1.8	2	12	9	25
11	27	1	2	2	1	15	20500	9300	1.7	2.5	2	15	8	24
12	35	2	1	2	1	13	3000	13400	2	1.5	2	16	9	22
13	41	2	2	2	2	9	21400	16300	5.8	4.9	1	31	17	11
14	26	1	1	2	1	11	1600	34000	5.3	4.7	1	34	16	15
15	41	1	0	1	1	15	2300	25000	1.5	1.3	2	5	4	42
16	29	1	1	2	2	10	23400	11700	8.4	5.3	1	33	21	12
17	53	2	2	2	1	8	2800	14200	12.4	5.6	1	36	22	10
18	56	2	0	1	1	15	6700	96000	1.4	1.8	2	4	5	42
19	34	1	1	1	1	13	18200	54000	2	1.5	2	12	8	25
20	28	1	1	1	1	14	2300	23600	1.5	1.9	2	13	9	21
21	43	1	2	2	2	7	21000	14500	4.5	5.3	1	34	18	12
22	47	1	2	2	2	9	1900	34000	6.3	7.2	1	37	20	10
23	25	2	1	1	1	14	16400	78000	1.5	1.9	2	15	8	24
24	48	1	1	1	1	14	2700	46000	1.7	1.9	2	13	9	27
25	51	2	0	2	1	15	3000	43000	0.8	1	2	5	5	48
26	32	1	1	2	2	10	23500	9200	4.7	6	1	38	22	11
27	57	1	2	2	1	8	17400	21000	7.5	4.6	1	36	20	12
28	22	1	0	1	1	15	2300	47000	0.7	0.8	2	4	3	45
29	44	2	1	2	1	14	15600	17500	1.8	1.4	2	13	7	24
30	34	2	1	2	1	13	2100	19000	1.9	1.2	2	12	8	25
31	46	1	0	2	1	14	4200	18600	1.7	1.3	2	10	8	26

32	57	1	1	1	2	12	2200	13500	2	1.7	2	14	9	22
33	58	2	2	2	1	7	21000	8600	3.6	4.9	1	34	17	13
34	20	1	1	2	1	9	24000	11800	7	4.5	1	33	18	11
35	23	1	0	1	1	15	15700	49000	0.8	1	2	3	3	40
36	54	1	1	1	1	15	10500	27000	0.6	0.9	2	5	3	45
37	38	2	1	2	1	8	24000	13200	7.3	4.9	1	36	17	10
38	48	2	1	2	1	10	1900	25000	6.3	3.4	1	34	18	13
39	41	1	1	2	2	10	17800	11300	5.2	3.6	1	30	17	11
40	51	1	2	2	1	6	19500	14500	4.3	6.1	1	32	19	10
41	34	2	1	1	2	12	9200	16700	3.4	5	1	35	16	14
42	52	1	2	2	1	11	19500	22000	4.5	3.8	1	32	17	13
43	35	1	0	1	2	13	1700	9000	1.4	1.2	2	14	8	29
44	22	1	0	1	2	14	2400	17500	1.8	1.9	2	12	7	28
45	39	2	1	1	1	15	4800	29000	1.1	1	2	4	4	39
46	54	1	1	1	1	15	5400	37000	1	0.6	2	4	3	42
47	35	1	2	2	1	10	22000	13400	4.9	6	1	29	17	10
48	21	1	2	2	1	6	1700	16000	3.7	5.2	1	36	20	11
49	46	1	1	2	2	10	17500	18200	7	4.3	1	34	16	14
50	43	2	0	1	1	14	3400	38000	1.5	1.2	2	8	5	28
51	23	2	1	1	1	13	3500	41000	2	1.3	2	8	6	28
52	59	1	1	2	1	7	25000	17000	6.2	4.2	1	38	18	12
53	49	1	2	2	2	10	2800	16400	4.9	6.5	1	34	18	13
54	32	1	2	1	2	14	3700	34000	2.6	1.9	2	7	7	22
55	28	2	1	1	1	15	5300	19000	0.8	0.9	2	4	4	46
56	34	2	0	1	1	15	17900	38000	0.7	1	2	4	3	45
57	47	1	1	2	2	9	26400	17800	8.2	2	1	36	20	10
58	29	1	2	2	1	5	1700	11000	5	6.2	1	34	18	13
59	34	1	2	2	1	7	16800	22000	9.2	5	1	32	17	11
60	57	1	0	2	1	13	2300	28000	2.1	1.9	2	12	7	30
61	51	2	1	2	1	13	14300	12500	2.8	3.1	2	8	7	25
62	32	1	2	1	2	12	2000	17600	3	4.2	2	15	12	18
63	46	1	2	2	1	9	17000	32000	8.3	2	1	28	14	20

64	42	1	2	2	2	12	2400	23000	5.4	6.7	2	30	16	12
65	53	2	1	1	1	15	6300	42000	1	0.9	2	4	3	43
66	27	2	1	1	1	15	7200	38000	1.2	0.7	2	3	3	40
67	58	1	1	2	1	6	1700	13500	4.9	3.6	1	38	18	10
68	48	1	1	2	1	8	18400	23000	8.1	2.4	1	34	16	11
69	26	1	0	1	2	13	2400	17200	2.4	1.9	2	28	15	18
70	38	2	1	1	2	15	20100	32000	3	2.6	2	20	10	22
71	31	1	1	2	1	7	8000	15600	6.4	4.5	1	32	17	13
72	46	1	1	2	1	8	16700	21000	3	4.8	1	34	15	12
73	52	2	1	1	1	12	7200	39000	2	2.4	2	10	8	24
74	56	2	2	1	1	15	17200	17000	1.9	2.8	2	8	7	27
75	39	1	0	1	1	15	2900	14300	0.8	0.9	2	4	4	42
76	54	1	1	2	1	8	11400	18200	6.2	4.7	1	34	16	11
77	43	1	2	2	1	6	21000	16000	9.7	4.2	1	36	15	10
78	29	1	2	1	2	14	3100	23000	1.1	0.8	2	6	4	24
79	53	2	1	1	2	13	18000	20800	1	0.6	2	8	4	25
80	28	1	0	1	1	15	17200	14500	1.1	0.8	2	3	3	41
81	54	1	1	1	1	15	6200	19000	0.8	1	2	4	4	39
82	27	1	1	2	2	6	14500	9000	7.3	5	1	36	18	13
83	36	2	1	2	1	8	23000	14600	4.2	3	1	32	15	14
84	52	1	0	2	1	14	3000	37000	1.8	2.3	2	12	7	25
85	42	1	1	1	1	13	2300	11000	2	1.9	2	10	6	24
86	52	1	2	1	1	14	11000	26000	2.4	1.6	2	12	8	25
87	28	1	1	2	2	13	15600	31000	1.7	3.2	2	13	7	27
88	21	1	2	1	1	4	24000	13200	7	5.3	1	34	18	10
89	44	2	1	1	2	6	1600	12000	6.2	7	1	36	17	13
90	44	2	1	1	1	15	4600	25000	0.7	0.9	2	4	3	43
91	53	1	1	1	1	14	5700	31000	0.9	1	2	5	3	39
92	26	1	1	1	1	14	6200	17000	0.6	1.1	1	5	4	35
93	43	1	0	1	2	12	13700	28000	2.3	1.5	2	14	7	25
94	56	2	2	1	1	13	17800	43000	2	3.6	2	16	9	23
95	51	2	1	1	1	14	2100	19000	1.1	1.9	2	13	8	24
96	42	1	1	2	1	13	3200	24000	1.8	2.4	2	14	8	26
97	48	1	1	2	2	10	23000	9200	4.9	5.2	2	36	17	14
98	35	1	1	2	1	8	17300	13000	5.3	6	1	38	19	10
99	45	2	2	2	1	5	1900	15400	8	3.4	1	34	20	11
100	56	1	1	2	1	7	24300	34600	4.8	5.8	1	32	18	13